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March 25, 2005

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APPLICATION NUMBER: *60/572,024*
FILING DATE: *May 18, 2004*

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

By Authority of the
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15992 U.S.PTO

PTO/SB/16(06-03)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 271824567 US

2151 U.S. PTO 60/572024 051804

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☒ *Additional inventors are being named on the 2 OF 2 separately numbered sheets attached hereto.*

TITLE OF THE INVENTION *(500 characters max)*

Novel Pharmaceuticals

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification	Number of Pages	88	☒ Claims	11	
☐ Drawing(s)	Number of Sheets		☒ Abstract	1	
☒ Application Data Sheet. See 37 CFR1.76		3			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

		FILING FEE AMOUNT($)
☐	Applicant claims small entity status. See 37 CFR1.27	
☐	A check or money order is enclosed to cover the filing fees	$160.00
☒	The Director is hereby authorized to charge all required filing fees to, and credit any overpayment to Deposit Account Number: **16-1445**	
☐	Payment by credit card Form PTO-2038 is attached.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE Christine S. Lee DATE: 5/18/04

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TELEPHONE 860-686-2144 Docket Number. PC32260

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

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PROVISIONAL APPLICATION COVER SHEET
Additional Page

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XPRESS MAIL NO. EV271824567 US

Docket Number **PC32260**

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Number 2 of 2

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Application Data Sheet
EXPRESS MAIL NO. EV 271824567 US

pplication Information

pplication Type::	Provisional
ubject Matter::	Utility
itle::	Novel Pharmaceuticals
ttorney Docket Number::	**PC32260**

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Novel Pharmaceuticals

The present invention relates to a series of novel 5,7-diaminopyrazolo[4,3-*d*] pyrimidines, which are cyclic guanylate monophosphate (cGMP)-specific phosphodiesterase type 5 inhibitors (hereinafter referred to as PDE-5 inhibitors) that are useful in the treatment of hypertension and other disorders, to processes for their preparation, intermediates used in their preparation, to compositions containing them and the uses of said compounds and compositions.

i) Hypertension

Blood pressure (BP) is defined by a number of haemodynamic parameters taken either in isolation or in combination. Systolic blood pressure (SBP) is the peak arterial pressure attained as the heart contracts. Diastolic blood pressure is the minimum arterial pressure attained as the heart relaxes. The difference between the SBP and the DBP is defined as the pulse pressure (PP).

Hypertension, or elevated BP, has been defined as a SBP of at least 140mmHg and/or a DBP of at least 90mmHg. By this definition, the prevalence of hypertension in developed countries is about 20% of the adult population, rising to about 60-70% of those aged 60 or more, although a significant fraction of these hypertensive subjects have normal BP when this is measured in a non-clinical setting. Some 60% of this older hypertensive population have isolated systolic hypertension (ISH), i.e. they have an elevated SBP and a normal DBP. Hypertension is associated with an increased risk of stroke, myocardial infarction, atrial fibrillation, heart failure, peripheral vascular disease and renal impairment (Fagard, RH; Am. J. Geriatric Cardiology 11(1), 23-28, 2002; Brown, MJ and Haycock, S; Drugs 59(Suppl 2), 1-12, 2000).

The pathophysiology of hypertension is the subject of continuing debate. While it is generally agreed that hypertension is the result of an imbalance between cardiac output and peripheral vascular resistance, and that most hypertensive subjects have abnormal cardiac output and increased peripheral resistance

there is uncertainty which parameter changes first (Beevers, G et al.; BMJ 322, 912-916, 2001).

Despite the large number of drugs available in various pharmacological categories, including diuretics, alpha-adrenergic antagonists, beta-adrenergic antagonists, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists, the need for an effective treatment of hypertension is still not satisfied.

ii) PDE5 inhibitors

Vascular endothelial cells secrete nitric oxide (NO). This acts on vascular smooth muscle cells and leads to the activation of guanylate cyclase and the accumulation of cyclic guanosine monophosphate (cGMP). The accumulation of cGMP causes the muscles to relax and the blood vessels to dilate. This dilation reduces vascular resistance and so leads to a reduction in blood pressure.

The cGMP is inactivated by hydrolysis to guanosine 5'-monophosphate (GMP) by a cGMP-specific phosphodiesterase. One important phosphodiesterase has been identified as Phosphodiesterase type 5 (PDE5). Inhibitors of PDE5 decrease the rate of hydrolysis of cGMP and so potentiate the actions of nitric oxide.

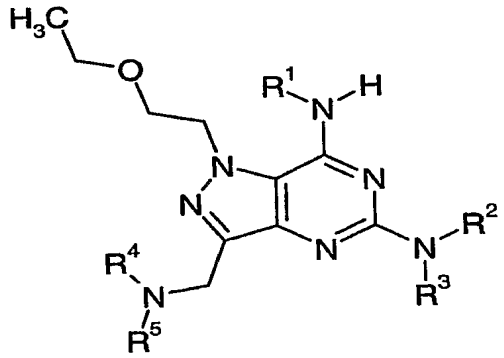
Inhibitors of PDE5 have been reported in several chemical classes, including: pyrazolo[4,3-d]pyrimidin-7-ones (e.g. published international patent applications WO 93/06104, WO 98/49166, WO 99/54333, WO 00/24745, WO 01/27112 and WO 01/27113); pyrazolo[3,4-d]pyrimidin-4-ones (e.g. published international patent application WO 93/07149); pyrazolo[4,3-d]pyrimidines (e.g. published international patent application WO 01/18004); quinazolin-4-ones (e.g. published international patent application WO 93/12095); pyrido[3,2-d]pyrimidin-4-ones (e.g. published international patent application WO 94/05661); purin-6-ones (e.g. published international patent application WO 94/00453); hexahydro-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-diones (e.g. published international

application WO 95/19978) and imidazo[5,1-f][1,2,4]triazin-ones (e.g. published international application WO 99/24433).

Although they have been suggested as agents for the treatment of related conditions such as angina, PDE5 inhibitors have not yet been adopted as agents for the treatment of hypertension. PDE5 inhibitors are known for the treatment of male erectile dysfunction, e.g. sildenafil, tadalafil and vardenafil. There remains a demand for new PDE5 inhibitors, particularly with improved pharmacokinetic and pharmacodynamic properties. The compounds provided herein are potent inhibitors of PDE5 that have improved selectivity *in vitro* and/or an extended half-life *in vivo*.

WO 02/00660 and WO 01/18004 disclose pyrazolo[4,3-d]pyrimidines with a PDE-5 inhibiting effect, which can be used for treating disorders of the cardiovascular system.

According to a first aspect, the present invention provides compounds of formula (I)



(I)

wherein

R^1 is a cyclic group R^A which is optionally substituted with one or more C_1-C_3 alkyl groups;

R^2 and R^3 are each independently hydrogen or C_1-C_3 alkyl optionally substituted with a group selected from OH and OCH_3;

R^4 is selected from R^6, $R^6C(O)$ and R^6SO_2, and

R^5 is selected from hydrogen and C_1-C_3 alkyl,

or $-NR^4R^5$ constitutes a 5- or 6-membered saturated ring which may optionally include one further heteroatom selected from nitrogen and oxygen, and which may optionally be substituted with a group selected from methyl, methoxy and methoxymethyl;

R^6 is selected from C_1-C_3 alkyl optionally substituted a group selected from hydroxy, methoxy and dimethylamino; and

R^A is a 6-membered heteroaromatic ring containing one or two nitrogen atoms;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer.

Unless otherwise indicated, an alkyl or alkoxy group may be straight or branched and contain 1 to 8 carbon atoms, preferably 1 to 6 and particularly 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, pentyl and hexyl. Examples of alkoxy include methoxy, ethoxy, isopropoxy and n-butoxy.

Unless otherwise indicated, an alkenyl or alkynyl group may be straight or branched and contain 2 to 8 carbon atoms, preferably 2 to 6 and particularly 2 to 4 carbon atoms and may contain up to 3 double or triple bonds which may be conjugated. Examples of alkenyl and alkynyl include vinyl, allyl, butadienyl and propargyl.

Unless otherwise indicated, a cycloalkyl or cycloalkoxy group may contain 3 to 10 ring-atoms, may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl and adamantyl.

Unless otherwise indicated, a cycloalkenyl group may contain 3 to 10 ring-atoms, may be either monocyclic or, when there are an appropriate number of ring atoms, polycyclic and may contain up to 3 double bonds. Examples of cycloalkenyl groups are cyclopentenyl and cyclohexenyl.

Aryl includes phenyl, naphthyl, anthracenyl and phenanthrenyl.

Unless otherwise indicated, a heteroalicyclyl group contains 3 to 10 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur, and may be saturated or partially unsaturated. Examples of heteroalicyclyl groups are oxiranyl, azetidinyl, tetrahydrofuranyl, thiolanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, sulfolanyl, dioxolanyl, dihydropyranyl, tetrahydropyranyl, piperidinyl, pyrazolinyl, pyrazolidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, azepinyl, oxazepinyl, thiazepinyl, thiazolinyl and diazapanyl.

Unless otherwise indicated, a heteroaryl group contains 3 to 10 ring-atoms up to 4 of which may be hetero-atoms such as nitrogen, oxygen and sulfur. Examples of heteroaryl groups are furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, tetrazolyl, triazinyl. In addition, the term heteroaryl includes fused heteroaryl groups, for example benzimidazolyl, benzoxazolyl, imidazopyridinyl, benzoxazinyl, benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, benzothiazolyl, phthalimido, benzofuranyl, benzodiazepinyl, indolyl and isoindolyl.

Halo means fluoro, chloro, bromo or iodo.

Haloalkyl includes monohaloalkyl, polyhaloalkyl and perhaloalkyl, such as 2-bromoethyl, 2,2,2-trifluoroethyl, chlorodifluoromethyl and trichloromethyl. Haloalkoxy includes monohaloalkoxy, polyhaloalkoxy and perhaloalkoxy, such as 2-bromoethoxy, 2,2,2-trifluoroethoxy, chlorodifluoromethoxy and trichloromethoxy. Halocycloalkyl includes monohalocycloalkyl, polyhalocycloalkyl and perhalocycloalkyl.

Unless otherwise indicated, the term substituted means substituted by one or more defined groups. In the case where groups may be selected from a number of alternative groups, the selected groups may be the same or different.

R^1 is preferably a cyclic group R^A, which is optionally substituted with a methyl group.

R^A is preferably a pyridyl, pyrimidinyl or pyrazinyl group.

Preferably, R^2 is C_1-C_3 alkyl optionally substituted with a group selected from OH and OCH_3 and R^3 hydrogen or C_1-C_3 alkyl. R^2 is more preferably methyl or ethyl optionally substituted at the 2-position with a group selected from OH and OCH_3. R^3 is more preferably hydrogen or methyl.

In one preferred embodiment, R^4 is selected from R^6, $R^6C(O)$ and R^6SO_2 and R^5 is selected from hydrogen and C_1-C_3 alkyl. In one more preferred embodiment, R^4 is R^6 and R^6 is C_1-C_3 alkyl or 2-methoxyethyl. In another more preferred embodiment R^4 is $R^6C(O)$ and R^6 is selected from methyl, ethyl, hydroxymethyl and dimethylaminomethyl. In another more preferred embodiment R^4 is R^6SO_2 and R^6 is methyl.

In another preferred embodiment $-NR^4R^5$ constitutes a 5- or 6-membered saturated ring which may optionally include one further heteroatom selected from nitrogen and oxygen, and which may optionally be substituted with a group selected from methyl, methoxy and methoxymethyl. More preferably $-NR^4R^5$ constitutes a pyrrolidine, morpholine or piperazine ring optionally be substituted with a group selected from methyl, methoxy and methoxymethyl.

Most preferred compounds are:

2-dimethylamino-*N*-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]methanesulfonamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-2-hydroxyacetamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide,

N-[1-(2-ethoxyethyl)-5-ethylamino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]propionamide,

N-[1-(2-ethoxyethyl)-5-ethylamino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]propionamide,

N-[1-(2-ethoxyethyl)-5-ethylamino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-methylacetamide,

1-(2-ethoxyethyl)-N^5,N^5-dimethyl-3-[(4-methylpiperazin-1-yl)methyl]-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine,

1-(2-ethoxyethyl)-N^5,N^5-dimethyl-3-[(4-morpholino)methyl]-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine, and

1-(2-ethoxyethyl)-3-(ethylaminomethyl)-N^5,N^5-dimethyl-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine

and tautomers thereof and pharmaceutically acceptable salts, solvates and polymorphs of said compounds or tautomers.

Pharmaceutically acceptable salts of the compounds of formula (I) include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionised, partially ionised, or non-ionised. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula (I) include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula (I) as hereinbefore defined, polymorphs, prodrugs, and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula (I).

As stated, the invention includes all polymorphs of the compounds of formula (I) as hereinbefore defined.

Also within the scope of the invention are so-called 'prodrugs' of the compounds of formula (I). Thus certain derivatives of compounds of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula (I) with

certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula (I) contains a carboxylic acid functionality (-COOH), an ester thereof, for example, replacement of the hydrogen with (C_1-C_8)alkyl;

(ii) where the compound of formula (I) contains an alcohol functionality (-OH), an ether thereof, for example, replacement of the hydrogen with (C_1-C_6)alkanoyloxymethyl; and

(iii) where the compound of formula (I) contains a primary or secondary amino functionality (-NH_2 or -NHR where R ≠ H), an amide thereof, for example, replacement of one or both hydrogens with (C_1-C_{10})alkanoyl.

Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

Finally, certain compounds of formula (I) may themselves act as prodrugs of other compounds of formula (I).

Compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula (I) contains an alkenyl or alkenylene group, geometric *cis*/*trans* (or Z/E) isomers are possible. Where the compound contains, for example, a keto or oxime group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures

of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% isopropanol, typically from 2 to 20%, and from 0 to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E L Eliel (Wiley, New York, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula (I) wherein one or more atoms are replaced by

atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labelled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

The compounds of formula (I) are inhibitors of PDE5. Accordingly, in a further aspect the present invention provides for the use of a compound of formula (I), or a tautomer, salt or solvate thereof, as a pharmaceutical agent, and particularly as a therapeutic agent for the treatment of a condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

The term "treatment" includes palliative, curative and prophylactic treatment.

Conditions suitable for treatment with the compounds of the invention include hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain),

cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

In a further aspect, the present invention provides for the use of a compound of formula (I), or a tautomer, salt or solvate thereof, for the manufacture of a medicament for the treatment of such a condition.

The compounds of the present invention may be used alone or in combination with other therapeutic agents. When used in combination with another therapeutic agent the administration of the two agents may be simultaneous or sequential. Simultaneous administration includes the administration of a single dosage form that comprises both agents and the administration of the two agents in separate dosage forms at substantially the same time. Sequential administration includes the administration of the two agents according to different schedules provided that there is an overlap in the periods during which the treatment is provided. Suitable agents with which the compounds of formula (I) can be co-administered include aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), CI1027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-

cyclopentyl)-acetic acid, (1α,3α,5α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid).

The compounds of formula (I) may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene

glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 wt% to 80 wt% of the dosage form, more typically from 5 wt% to 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 wt% to 25 wt%, preferably from 5 wt% to 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 wt% to 5 wt% of the tablet, and glidants may comprise from 0.2 wt% to 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium

stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 wt% to 10 wt%, preferably from 0.5 wt% to 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets, Vol. 1", by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-6918-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et al*, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal,

intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may

be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (*e.g.* Powderject™, Bioject™, *etc.*) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as *l*-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1µg to 10mg of the compound of the invention per actuation and the actuation volume may vary from 1µl to 100µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1µg to 20mg of the compound of formula (I). The overall daily dose will typically be in the range 1µg to 80mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (*e.g.* absorbable gel sponges, collagen) and non-biodegradable (*e.g.* silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion

complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula ... in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

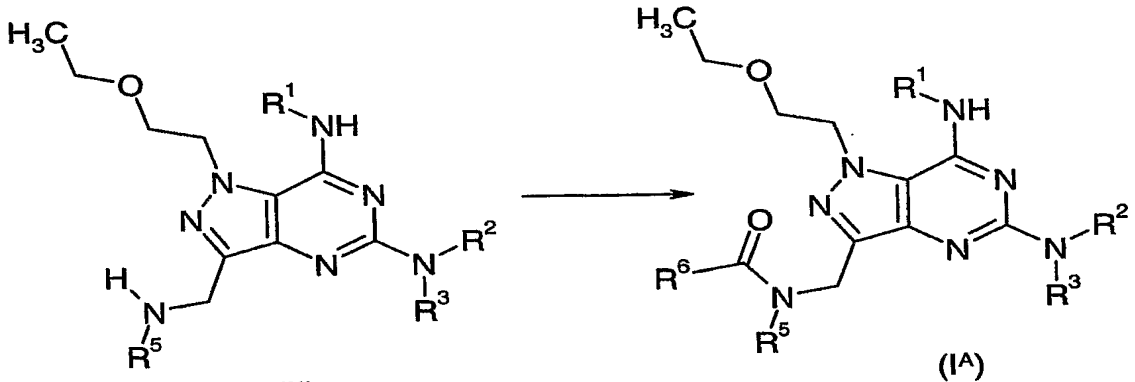
For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.1mg to 500 mg depending, of course, on the mode of administration. For example, oral administration may require a total daily dose of from 0.1 mg to 500 mg, while an intravenous dose may only require from 0.01mg to 50mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

Compounds of the invention may be prepared, in known manner in a variety of ways. In the following reaction schemes and hereafter, unless otherwise stated R^1 to R^{18} are as defined in the first aspect. These processes form further aspects of the invention.

a) Compounds of formula (I^A), i.e. compounds of formula (I) wherein R^4 is $R^6C(O)$ can be prepared by acylation of the corresponding compounds of formula (II), as illustrated in Scheme 1.

Scheme 1



(II) (I^A)

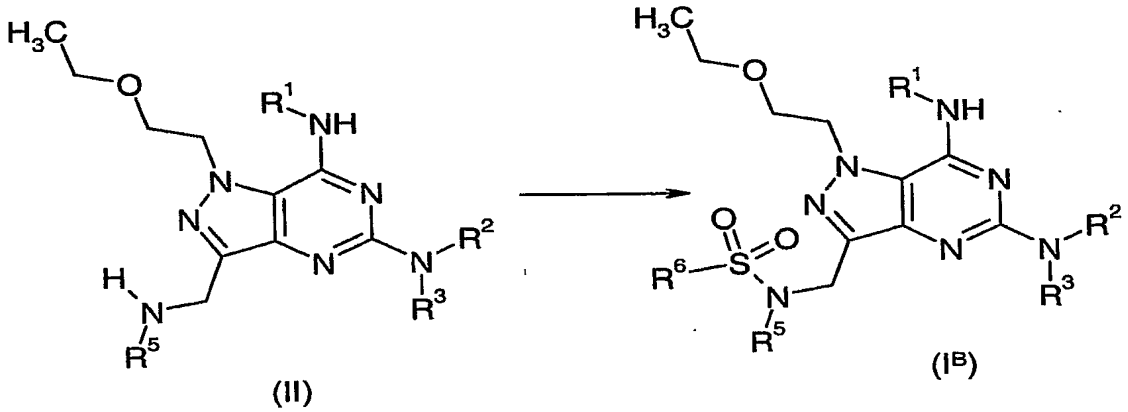
The compound of formula (II) is treated with 1-2 equivalents of an acylating agent such as an acyl chloride $R^6C(O)Cl$ or an anhydride $(R^6C(O))_2O$ in a suitable solvent in the presence of a tertiary amine base such as triethylamine, N-ethyldiisopropylamine or pyridine. Suitable solvents include dichloromethane and dimethylformamide. Preferably, the compound of formula (II) is treated with about 1.3 equivalents of acyl chloride and about 1.3 equivalents of triethylamine in dichloromethane for 18 hours.

Alternatively, a mixture of the compound of formula (II) and an acid R^6COOH in a suitable solvent is treated with a condensing agent, optionally in the presence of 1-hydroxybenzotriazole (HOBT) (or 1-hydroxy-7-azabenzotriazole (HOAT))

and a tertiary amine base such as triethylamine, N-ethyldiisopropylamine or 4-(dimethylamino)pyridine, at a temperature of between 0ºC and the boiling point of the solvent. Suitable solvents include acetonitrile, dichloromethane, dimethylformamide, ethyl acetate, N-methylpyrrolidinone, tetrahydrofuran and mixtures thereof. Suitable condensing agents include: 1,1'-carbonyldiimidazole, carbodiimides such as dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylaminopropyl)-1-ethylcarbodiimide (WSCDI); uronium salts such as *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU); phosphonium salts such as 1-benzotriazolyloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) and 1-benzotriazolyloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP); diphenylphosphinic chloride (Dpp-Cl) and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl). Preferably, an equimolar solution of the compound of formula (ID) and the acid in dichloromethane is treated with about 1.1 equivalents of HATU and about 1.5 equivalents of N-ethyldiisopropylamine at room temperature for 18 hours.

b) Compounds of formula (I^B), i.e. compounds of formula (I) wherein R^4 is R^6SO_2 can be prepared by sulfonylation of the corresponding compounds of formula (II), as illustrated in Scheme 2.

Scheme 2



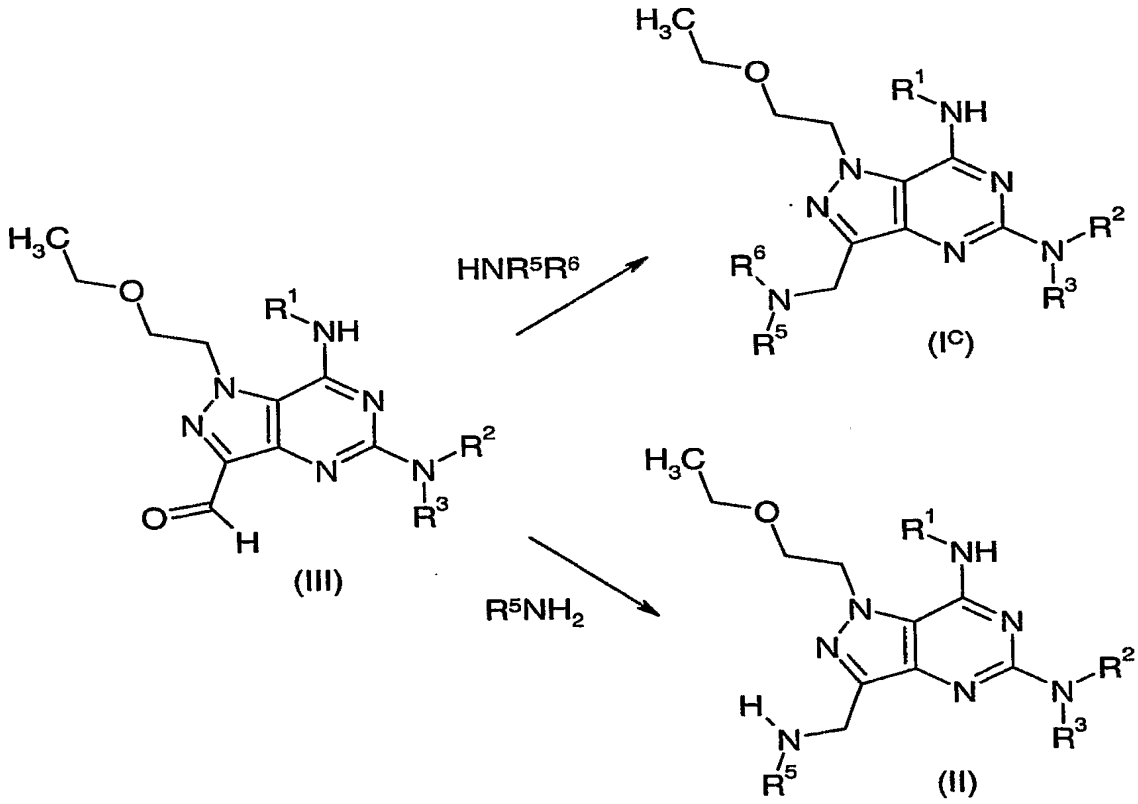
(II) (I^B)

The compound of formula (II) is treated with 1-2 equivalents of a sulfonyl chloride R^6SO_2Cl in a suitable solvent in the presence of a tertiary amine base such as triethylamine, N-ethyldiisopropylamine or pyridine. Suitable solvents

include dichloromethane and dimethylformamide. Preferably, the compound of formula (II) is treated with about 1.1 equivalents of sulfonyl chloride and about 1.5 equivalents of N-ethyldiisopropylamine in dichloromethane for 18 hours.

c) Compounds of formula (I^C), i.e. compounds of formula (I) wherein R^4 is R^6, and compounds of formula (II) may be prepared by reductive amination of an aldehyde of formula (III) with an amine HNR^5R^6 or R^5NH_2 respectively, as illustrated in Scheme 3.

Scheme 3

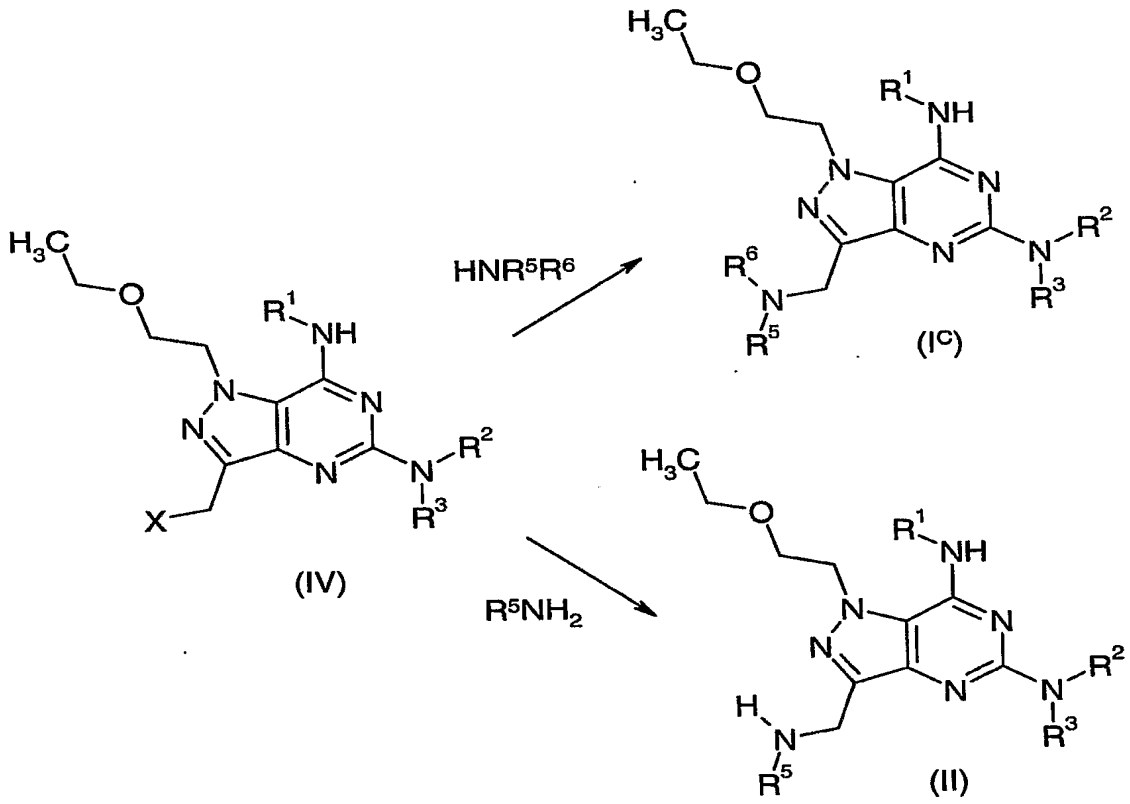


A solution of the amine and the aldehyde in a suitable solvent is treated with a reducing agent such as sodium cyanoborohydride ($NaBH_3CN$) or sodium tri(acetoxy)borohydride ($Na(AcO_3)BH$), optionally in the presence of acetic acid, at a temperature of between 0°C and the boiling point of the solvent, for 1hour to 24hours. Suitable solvents include alcohols, particularly methanol and ethanol.

This method is also suitable for the preparation of compounds of formula (I) wherein $-NR^4R^5$ constitutes a saturated ring. The appropriate amine HNR^4R^5 is used in place of the amine HNR^5R^6.

d) Compounds of formula (I^C) and compounds of formula (II) may also be prepared by reaction of a chloride or bromide of formula (IV), wherein X is a leaving group such as Cl, Br or CH_3SO_2O-, with an amine HNR^5R^6 or R^5NH_2 respectively, as illustrated in Scheme 4.

Scheme 4

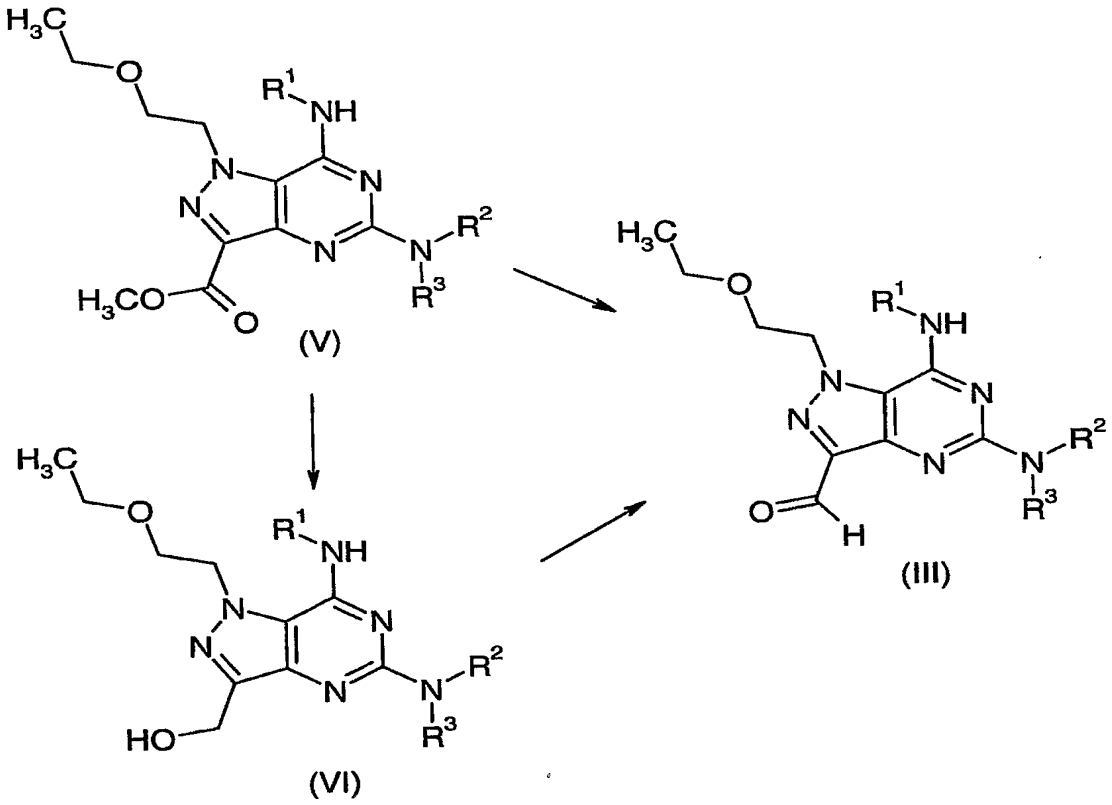


A solution of the amine and the compound of formula (IV) in a suitable solvent, optionally in the presence of a base such as a tertiary amine (for example N-ethyldiisoprpylamine) or an alkali metal carbonate (for example potassium carbonate), is stirred at a temperature of between 0°C and the boiling point of the solvent, for 1hour to 24hours. Suitable solvents include tetrahydrofuran, dimethylformamide and dimethylsulfoxide. Preferably the leaving group X is Br or Cl, and more preferably it is Cl.

This method is also suitable for the preparation of compounds of formula (I) wherein $-NR^4R^5$ constitutes a saturated ring. The appropriate amine HNR^4R^5 is used in place of the amine HNR^5R^6.

e) Compounds of formula (III) can be prepared from the esters of formula (V) either directly or, more preferably, via the corresponding alcohols of formula (VI) by the methods illustrated in Scheme 5.

Scheme 5



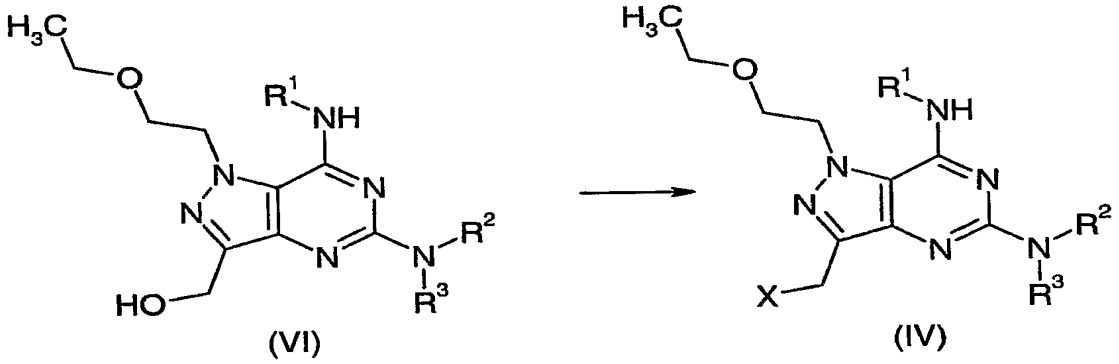
The reduction of the esters of formula (V) to give the aldehydes of formula (III) may be achieved using diisobutylaluminium hydride (DIBAL) in a suitable solvent at a temperature of less than 0°C, preferably less than -60°C. Suitable solvents include hydrocarbons such as pentane, hexane and toluene, ethers such as tetrahydrofuran, and mixtures thereof. The use of excess DIBAL or higher temperatures generally results in the production of the alcohols of formula (VI).

These alcohols may also be produced using other reducing agents such as lithium aluminiumhydride or lithium borohydride.

The oxidation of the alcohols of formula (VI) can be achieved using a chromium(VI) reagent such as pyridinium chlorochromate, a hypervalent iodine reagent such as the Dess-Martin periodinane, or a combination of tetra-n-propylammonium perruthenate and N-methylmorpholine-N-oxide in a suitable solvent at a temperature of between 0°C and ambient temperature. Suitable solvents include dichloromethane. The use of Dess-Martin periodinane is preferred.

f) Compounds of formula (IV) can be prepared from the corresponding alcohols of formula (VI) by the method illustrated in Scheme 6.

Scheme 6

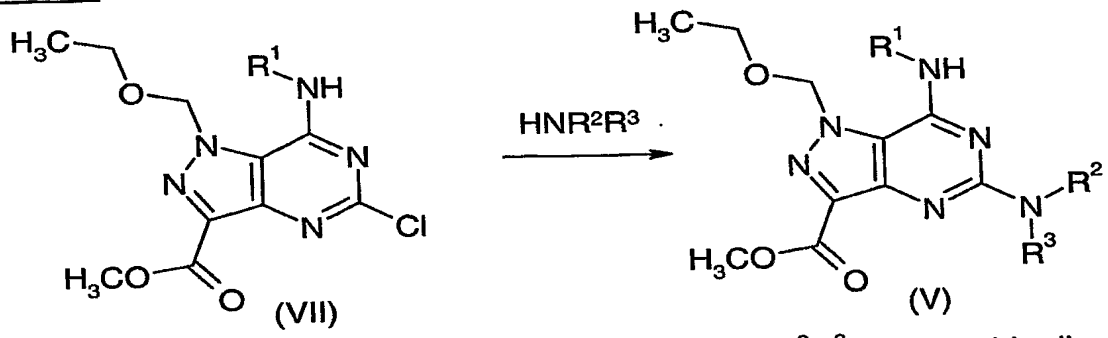


Compounds of formula (IV) wherein X is Cl may be prepared by treating the alcohol of formula (VI) with a mixture of triphenylphosphine and N-chlorosuccinimide or tetrachloromethane, or with thionyl chloride. Suitable solvents include dichloromethane and tetrahydrofuran. The analogous compounds wherein X is Br may be prepared by reaction with a mixture of triphenylphosphine and N-bromosuccinimide, bromine, or tetrabromomethane.

Compounds of formula (IV) wherein X is an alkylsulfonate, such as CH_3SO_2O-, may be prepared by treating the alcohol with the corresponding alkylsulfonyl chloride in the presence of a tertiary amine base.

g) Compounds of formula (V) can be prepared from the corresponding monochlorides of formula (VII) by reaction with HNR^2R^3 as illustrated in Scheme 7.

Scheme 7

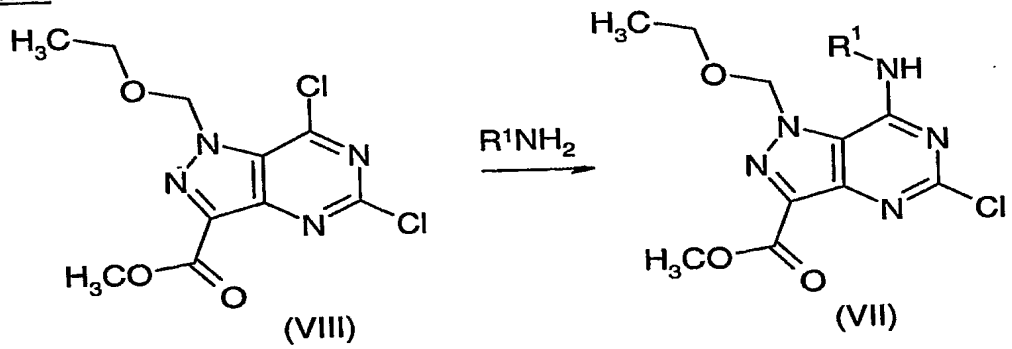


A solution of the monochloride (VII) and the amine HNR^2R^3 in a suitable dipolar aprotic solvent are stirred at elevated temperature for between 1 and 24 hours. Suitable solvents include dimethylsulfoxide, dimethylformamide and N-methylpyrrolidinone. An excess of a tertiary amine such as N-ethyldiisopropylamine, N-methylmorpholine or triethylamine may optionally be included. It is sometimes necessary to perform the reaction at elevated pressure in a closed vessel, particularly when the amine HNR^2R^3 or the solvent is volatile.

Preferably, the monochloride is treated with 1-5 equivalents of the amine HNR^2R^3 and optionally 3-5 equivalents of N-ethyldiisopropylamine in dimethylsulfoxide or N-methylpyrrolidinone at 100-125°C for 12-18 hours, in a sealed vessel.

h) Compounds of formula (VII) can be prepared from the dichloride of formula (VIII) by reaction with R^1NH_2 as illustrated in Scheme 8.

Scheme 8



(VIII) (VII)

A solution of the dichloride (VIII), the amine R^1NH_2 and an excess of a tertiary amine such as N-ethyldiisopropylamine, N-methylmorpholine or triethylamine in a suitable dipolar aprotic solvent are stirred at ambient or elevated temperature for between 1 and 24 hours. Suitable solvents include dimethylsulfoxide, dimethylformamide and N-methylpyrrolidinone. Preferably, the monochloride is treated with 2-5 equivalents of the amine R^1NH_2 and optionally 2-5 equivalents of N-ethyldiisopropylamine in dimethylsulfoxide or a mixture of dimethylsulfoxide and N-methylpyrrolidinone at 30-90°C for 1-18 hours.

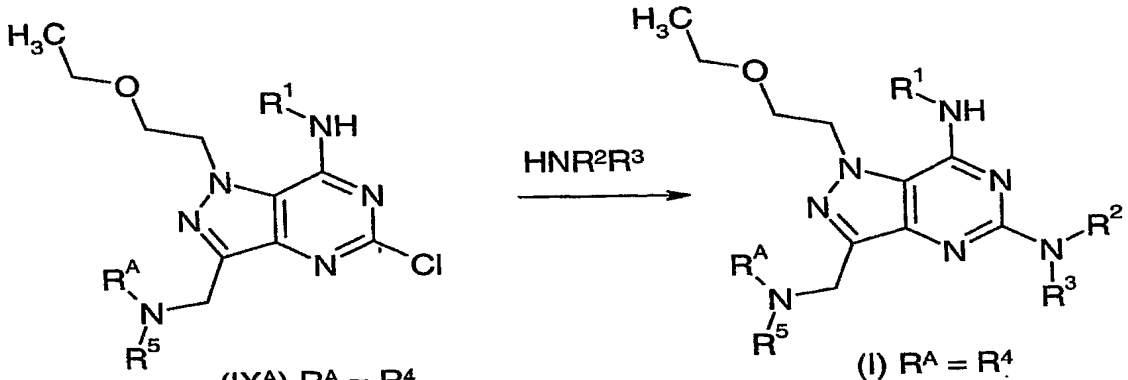
Alternatively, a solution of the amine R^1NH_2 in a suitable solvent is treated with butyllithium or sodium hexamethyldisilazide at low temperature, and the dichloride is added to the resulting solution. Suitable solvents include tetrahydrofuran and dioxan.

With less reactive amines R^1NH_2 this reaction can be low-yielding. In such cases it is sometimes advantageous to use an alternative strategy, as discussed in part l) below.

The preparation of the dichloride of formula (VIII) is described in detail in the Examples.

i) In a variation of the foregoing strategy, the compounds of formulae (I) and (II) may be prepared from monochlorides of formulae (IX^A) and (IX^B) repectively, as illustrated in Scheme 9

Scheme 9



(IX^A) $R^A = R^4$

(IX^B) $R^A = H$

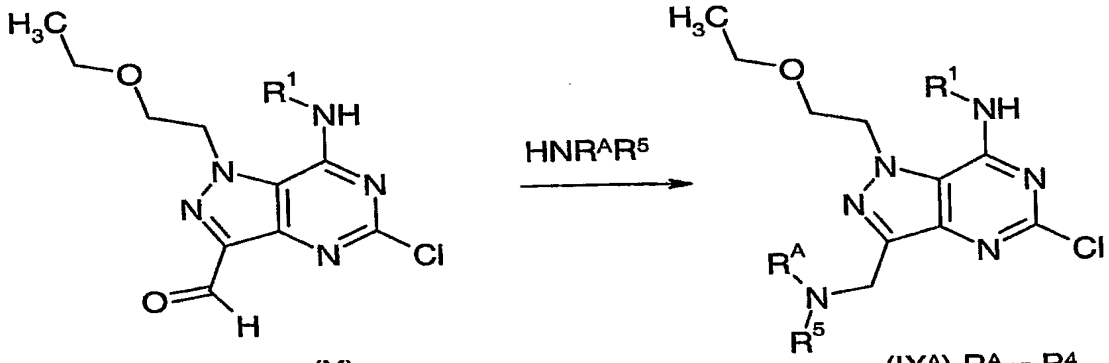
(I) $R^A = R^4$

(II) $R^A = H$

The transformation is accomplished as described in part g) above.

j) The compounds of formulae (IX^A) and (IX^B) may be prepared from the corresponding aldehydes of formula (X) or the alkylating agents of formula (XI) by the methods illustrated in Schemes 10A and 10B (wherein X has the same meaning as defined in part d) above) respectively.

Scheme 10A



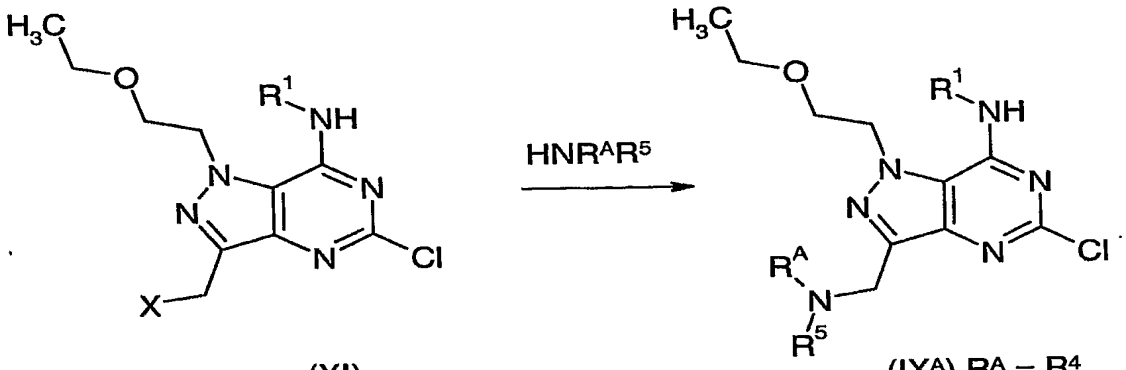
(X)

(IX^A) $R^A = R^4$

(IX^B) $R^A = H$

The transformation is accomplished as described in part c) above.

Scheme 10B



(XI)

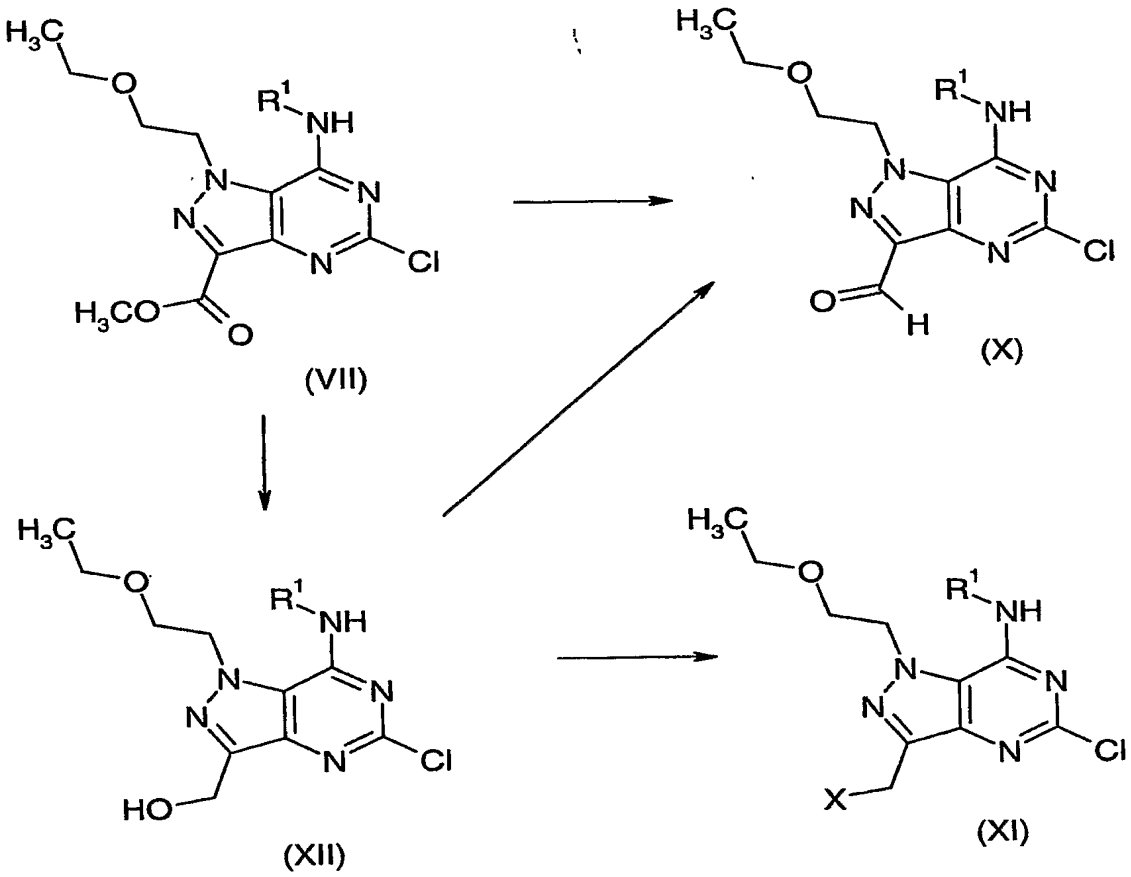
(IX^A) $R^A = R^4$

(IX^B) $R^A = H$

The transformation is accomplished as described in part d) above.

k) The compounds of formula (X) and (XI) can be prepared from the esters of formula (VII) as illustrated in Scheme 11.

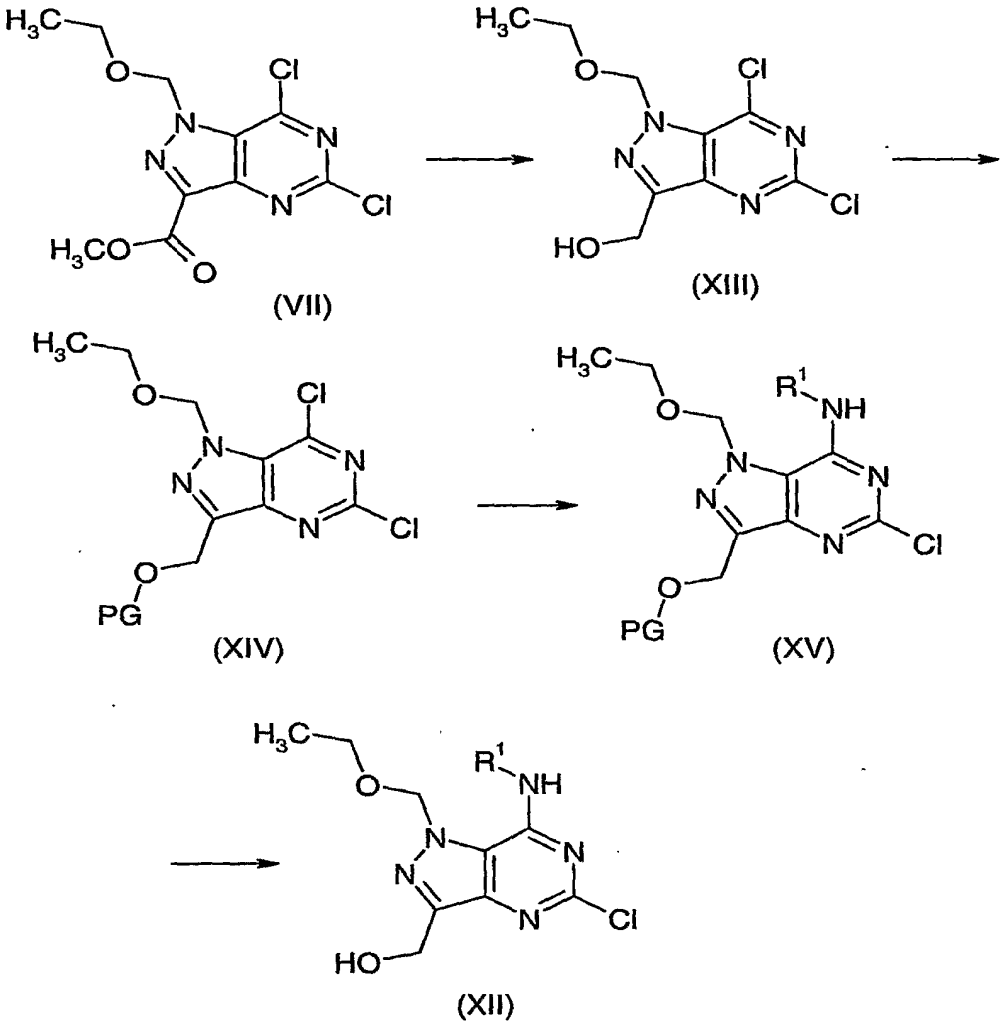
Scheme 11



The aldehydes of formula (X) may be prepared by limited reduction of the ester group or indirectly via the alcohols of formula (XII) using the methods described in part e) above. The compounds of formula (XI) can be prepared from the alcohols of formula (XII) using the methods described in part f) above.

l) As mentioned in part h) above, the reaction of compounds of formula (VIII) with weakly nucleophilic amines R^1NH_2 is sometimes not high yielding. An alternative route is illustrated in Scheme 12.

Scheme 12

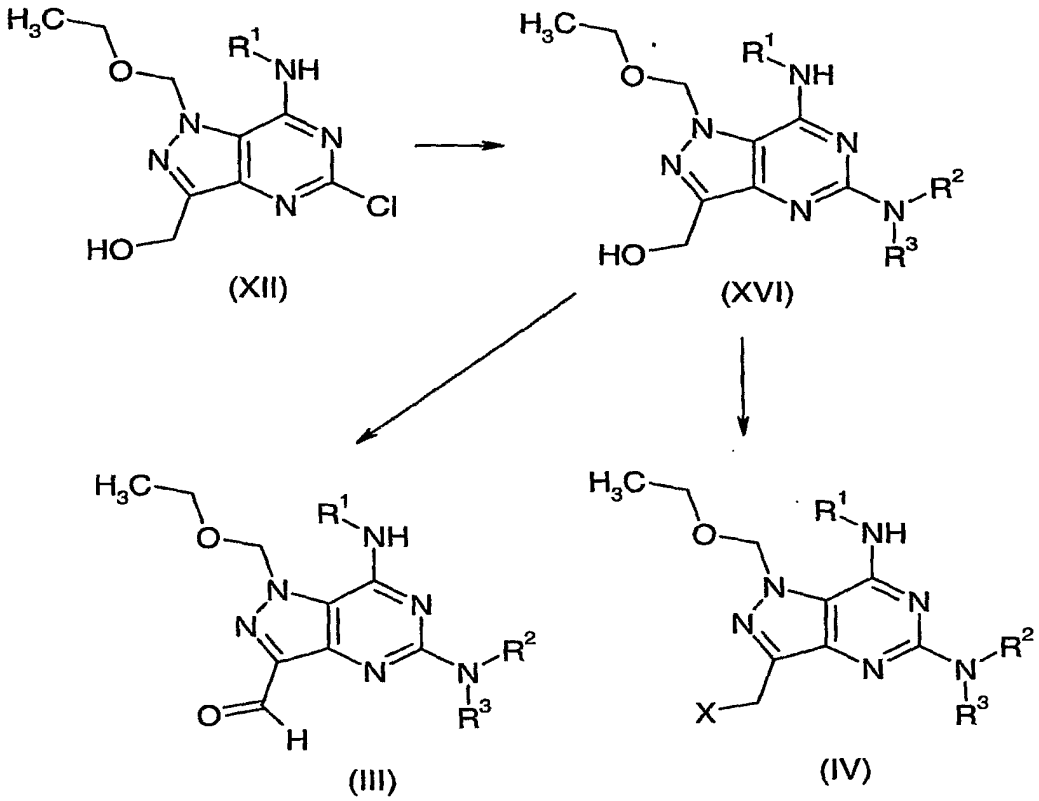


The reduction of the ester of formula (VII) is described in detail in the Examples. The primary alcohol (XIII) is then protected to give compounds of formula (XIV), wherein PG is an alcohol protecting group. A preferred protecting group is a trialkylsilyl group, particularly a *tert*-butyldimethylsilyl group. The compounds of formula (XIV) are then reacted with an amine R^1NH_2 according to the method described in part h) above to give compounds of formula (XV). Finally, the compounds of formula (XV) are deprotected to provide the primary alcohols of formula (XII) using appropriate conditions. When PG is a trialkylsilyl group it may be removed by treatment with a fluoride salt, such as tetrabutylammonium

fluoride, or with hydrochloric acid. The alcohols of formula (XII) may then be further elaborated as described in parts k), j) and i) above.

m) In a further variation, the alcohols of formula (XII) may be elaborated following the route illustrated in Scheme 13.

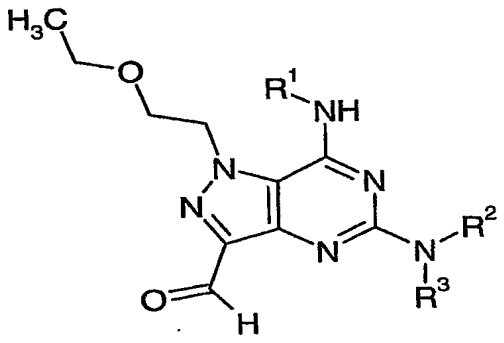
Scheme 13



The $-NR^2R^3$ group may be introduced according to the methods described in part g) above to provide compounds of formula (XVI). The primary alcohol group may then be oxidised as described in part e) above to provide the aldehydes of formula (III), or derivatised as described in part f) above to provide the compounds of formula (IV).

The following compounds form further aspects of the present invention:

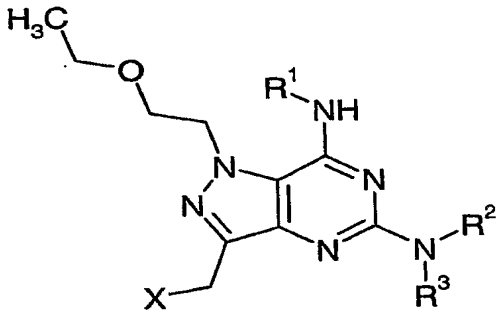
A compound of formula (III)



(III)

wherein R^1, R^2 and R^3 are as defined above.

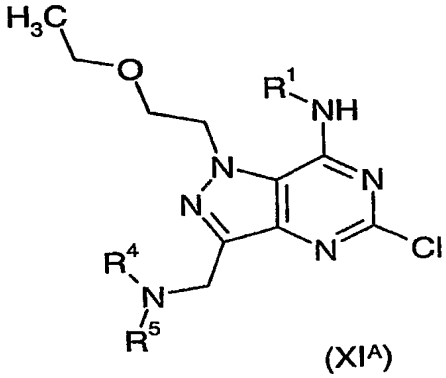
A compound of formula (IV)



(IV)

wherein R^1, R^2 and R^3 are as defined above and X is Cl, Br or CH_3SO_2O-.

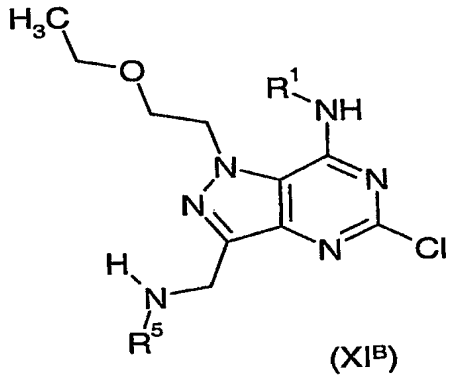
A compound of formula (XI^A)



(XI^A)

wherein R^1, R^4 and R^5 are as defined above.

A compound of formula (XI^B)



(XI^B)

wherein R^1 and R^5 are as defined above.

The invention is further illustrated by the following, non-limiting examples. Melting points were determined on a Gallenkamp melting point apparatus using glass capillary tubes and are uncorrected. Unless otherwise indicated all reactions were carried out under a nitrogen atmosphere, using commercially available anhydrous solvents. '0.88 Ammonia' refers to commercially-available aqueous ammonia solution of about 0.88 specific gravity. Thin-layer chromatography was performed on glass-backed pre-coated Merck silica gel (60 F254) plates, and silica gel column chromatography was carried out using 40-63μm silica gel (Merck silica gel 60). Ion exchange chromatography was performed using with the specified ion exchange resin which had been pre-washed with deionised water. Proton NMR spectra were measured on a Varian Inova 300, Varian Inova 400, or Varian Mercury 400 spectrometer in the solvents specified. In the NMR spectra, only non-exchangeable protons which appeared distinct from the solvent peaks are reported. Low resolution mass spectra were recorded on either a Fisons Trio 1000, using thermospray positive ionisation, or a Finnigan Navigator, using electrospray positive or negative ionisation. High resolution mass spectra were recorded on a Bruker Apex II FT-MS using electrospray positive ionisation. Combustion analyses were conducted by Exeter Analytical UK. Ltd., Uxbridge, Middlesex. Optical rotations were determined at 25°C using a Perkin Elmer 341 polarimeter using the solvents and concentrations specified. Example compounds designated as (+) or (-) optical

isomers are assigned based on the sign of optical rotation when determined in a suitable solvent.

Abbreviations, Definitions and Glossary

AcOH	acetic acid
Amberlyst® 15	Ion exchange resin, available from Aldrich Chemical Company
APCI	Atmospheric Pressure Chemical Ionisation
Arbocel™	Filtration agent, from J. Rettenmaier & Sohne, Germany
atm	Pressure in atmospheres (1 atm = 760 Torr = 101.3 kPa)
Biotage™	Chromatography performed using Flash 75 silica gel cartridge, from Biotage, UK
BOC	*tert*-butoxycarbonyl
br	Broad
c	Concentration used for optical rotation measurements in g per 100 ml (1 mg/ml is *c* 0.10)
cat	Catalytic
CBz	benzyloxycarbonyl
CDI	N,N'-carbonyldiimidazole
d	Doublet
DCC	N,N'-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	Doublet of doublets
DEAD	diethyl azodicarboxylate
Degussa® 101	10 wt% palladium on activated carbon, Degussa type E101 available from Aldrich Chemical Company
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one
Develosil Combi-RP C_{30} hplc column	Supplied by Phenomenex - manufactured by Nomura Chemical Co. Composed of spherical silica particles (size 3 µm or 5 µm) which have a chemically bonded surface of C30 chains. These particles are packed into stainless steel columns of dimensions 2 cm internal diameter and 25 cm long.
DIAD	diisopropyl azodicarboxylate

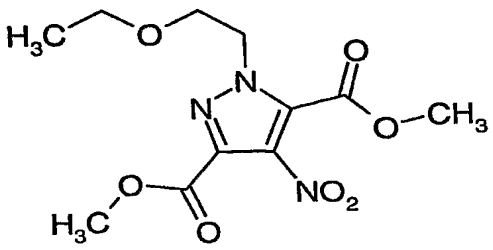
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
Dowex®	Ion exchange resin, from Aldrich Chemical Company
ee	Enantiomeric excess
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
HOAT	1-hydroxy-7-azabenzotriazole
HOBT	1-hydroxybenzotriazole hydrate
HRMS	High Resolution Mass Spectrocopy (electrospray ionisation positive scan)
Hünig's base	N-ethyldiisopropylamine
Hyflo™	Hyflo supercel®, from Aldrich Chemical Company
KHMDS	potassium bis(trimethylsilyl)amide
liq	Liquid
LRMS	Low Resolution Mass Spectroscopy (electrospray or thermospray ionisation positive scan)
LRMS (ES^-)	Low Resolution Mass Spectroscopy (electrospray ionisation negative scan)
m	Multiplet
m/z	Mass spectrum peak
MCI™ gel	High porous polymer, CHP20P 75-150μm, from Mitsubishi Chemical Corporation
MeOH	methanol
Mukaiyama's reagent	2-chloro-1-methylpyridinium iodide
NaHMDS	sodium bis(trimethylsilyl)amide
NMM	N-methylmorpholine
NMO	4-methylmorpholine *N*-oxide
NMP	1-methyl-2-pyrrolidinone
Phenomenex Luna C18 hplc	Supplied by Phenomenex. Composed of spherical silica particles (size 5 μm or 10 μm) which have a chemically bonded surface of

column	C18 chains. These particles are packed into a stainless steel column of dimensions 2.1cm internal diameter and 25 cm long.
psi	Pounds per square inch (1 psi = 6.9 kPa)
PyBOP®	Benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate
PyBrOP®	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	Quartet
R_f	Retention factor on TLC
s	Singlet
Sep-Pak®	Reverse phase C_{18} silica gel cartridge, Waters Corporation
t	Triplet
TBDMS-Cl	*tert*-butyldimethylchlorosilane
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS-Cl	chlorotrimethylsilane
WSCDI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
δ	Chemical shift

The following Examples illustrate the preparation of the compounds of the formula (I):-

Preparation 1

Dimethyl 1-(2-ethoxyethyl)-4-nitro-1*H*-pyrazole-3,5-dicarboxylate



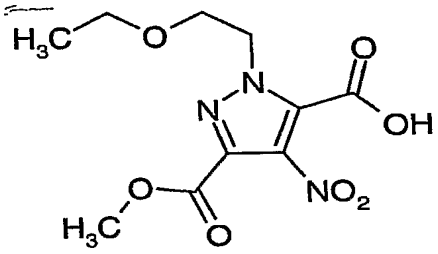
Potassium carbonate (1.32g, 9.57mmol) and 2-ethoxyethyl bromide (1.18mL, 9.57mmol) were added to a solution of dimethyl 4-nitro-1*H*-pyrazole-3,5-dicarboxylate (EP 1241170, pg. 50, preparation 10) (2g, 9.57mmol) in N,N-

dimethylformamide (35mL) and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200mL) and water (100mL). The organic phase was dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with pentane:ethyl acetate 100:0 to 70:30 in 10% increments to yield the title product, 1.63g.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.07 (t, 3H), 3.41 (m, 2H), 3.73 (t, 2H), 3.89 (s, 3H), 3.94 (s, 3H), 4.76 (t, 2H). MS APCI+ m/z 302 $[MH]^+$

Preparation 2

1-(2-Ethoxyethyl)-4-nitro-1*H*-pyrazole-3,5-dicarboxylic acid 3-methyl ester

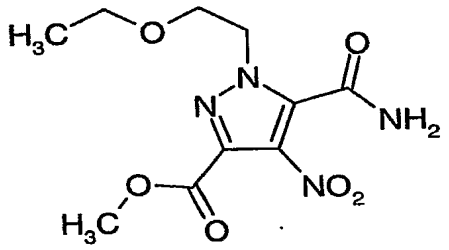


The di-ester of preparation 1 (1.63g, 5.4mmol) was added to a solution of potassium hydroxide (300mg, 5.9mmol) in methanol (20mL) and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in water (100mL) and washed with ether. The aqueous phase was acidified with 2M hydrochloric acid and extracted with dichloromethane (3x100mL). The organic phases were combined, dried over magnesium sulphate and concentrated *in vacuo* to yield the title product, 1.34g.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.07 (t, 3H), 3.47 (m, 2H), 3.80 (t, 2H), 3.88 (s, 3H), 4.77 (t, 2H). MS APCI+ m/z 288 $[MH]^+$

Preparation 3

Methyl 5-carbamoyl-1-(2-ethoxyethyl)-4-nitro-1*H*-pyrazole-3-carboxylate

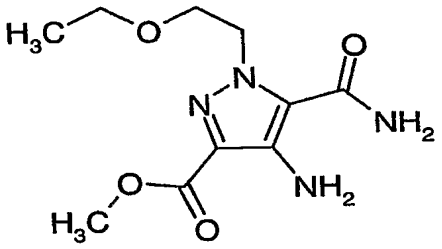


Oxalyl chloride (15.7mL, 190mmol) was added steadily to a solution of the carboxylic acid of preparation 2 (17.1g, 59.5mmol) in dichloromethane (300mL). N,N-Dimethylformamide (46µL, 6mmol) was then added and the reaction mixture stirred for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue azeotroped with dichloromethane (3x200mL). The product was dissolved in tetrahydrofuran (300mL), the solution cooled in ice, treated with 0.88 ammonia (200mL) and stirred for 18 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between water (200mL) and ethyl acetate. The organics were dried over magnesium sulphate and concentrated *in vacuo* to yield the crude product which was triturated from ether to yield the title product, 8.2g.

^{1}H NMR (DMSO-D_6, 400MHz) δ: 1.03 (t, 3H), 3.38 (m, 2H), 3.70 (t, 2H), 3.86 (s, 3H), 4.36 (t, 2H), 8.30 (m, 1H), 8.46 (m, 1H). MS APCI+ m/z 287 $[MH]^+$

Preparation 4

Methyl 4-amino-5-carbamoyl-1-(2-ethoxyethyl)-1*H*-pyrazole-3-carboxylate



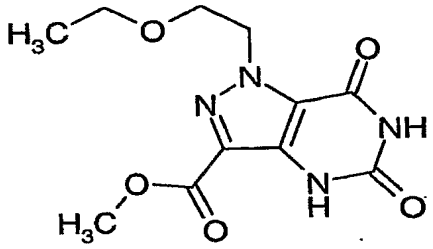
Palladium(II) hydroxide on carbon (1g) was added to a solution of the nitro compound of preparation 3 (8.2g, 28.6mmol) in methanol (300mL). Ammonium formate (8.8g, 0.14mol) was added portionwise to the reaction mixture over 20 minutes and the reaction mixture then stirred at reflux for 2 hours. The reaction was cooled to room temperature and filtered to remove catalyst. The filtrate was

concentrated *in vacuo* and azeotroped with toluene to yield the title product, 7.3g.

^{1}H NMR (DMSO-D_6, 400MHz) δ: 1.04 (t, 3H), 3.32 (m, 2H), 3.66 (t, 2H), 3.78 (s, 3H), 4.49 (t, 2H), 5.12 (m, 2H), 7.50 (m, 2H). MS APCI+ m/z 257 $[MH]^+$

Preparation 5

Methyl 1-(2-ethoxyethyl)-5,7-dioxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate

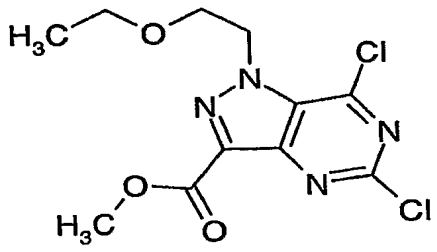


N,N'-Carbonyldiimidazole (5.54g, 34.2mmol) was added to a solution of the amide of preparation 4 (7.3g, 28.5mmol) in N,N-dimethylformamide (250mL) and the reaction mixture stirred at room temperature for 1 hour and then at 90°C for 18 hours. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was sonicated in acetone (200mL), the resulting solid filtered off and dried *in vacuo* to yield the title product, 5.3g.

^{1}H NMR (DMSO-D_6, 400MHz) δ: 0.99 (t, 3H), 3.37 (m, 2H), 3.77 (t, 2H), 3.82 (s, 3H), 4.64 (t, 2H). MS ES- m/z 281 $[M-H]^-$

Preparation 6

Methyl 5,7-dichloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate



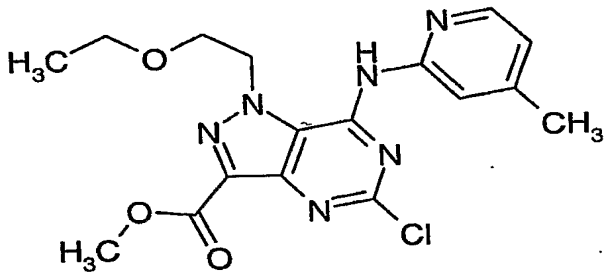
Phosphorous oxychloride (6.5mL, 70mmol) and tetraethylammonium chloride (3.47g, 21mmol) were added to a solution of the dione of preparation 5 (1.97g, 7mmol) in propionitrile (28mL) and the reaction mixture heated under reflux for 4 hours. Additional phosphorous oxychloride (2.5mL, 26.9mmol) was added and

the reaction mixture was then stirred under reflux for 18 hours. The reaction mixture was then concentrated *in vacuo* and the residue partitioned between dichloromethane (300mL) and water (50mL). The organics were separated, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate:pentane 0:100 to 25:75 to yield the title product, 1.98g.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.03 (t, 3H), 3.40 (m, 2H), 3.87 (t, 2H), 4.06 (s, 3H), 4.98 (t, 2H). MS APCI+ m/z 319 $[MH]^+$

Preparation 7

Methyl 5-chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate



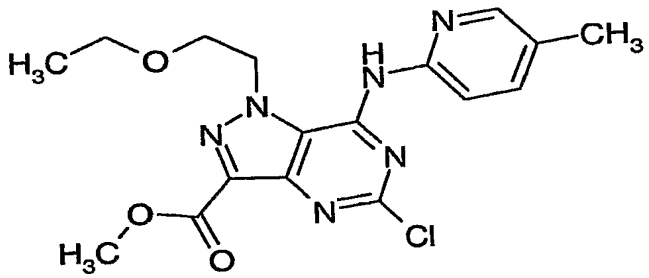
2-Amino-4-methylpyridine (1.34g, 12.4mmol) was added to a solution of the dichloro compound of preparation 6 (1.98g, 6.2mmol) in dimethyl sulphoxide (10mL) and the reaction stirred at 35°C for 5 hours. The reaction mixture was partitioned between dichloromethane (300mL) and water (500mL). The organics were separated, washed with water (3x100mL), dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel, eluting with dichloromethane:acetonitrile 98:2. Appropriate fractions were concentrated *in vacuo*, triturated with ether (50mL), filtered and the solid dried to yield the title product, 1.2g.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.06 (t, 3H), 2.49 (s, 3H), 3.62 (m, 2H), 4.00 (t, 2H), 4.06 (s, 3H), 5.05 (m, 2H), 6.98 (m, 1H), 8.16 (m, 1H), 8.50 (m, 1H).

MS APCI+ m/z 391 $[MH]^+$

Preparation 8

Methyl 5-chloro-1-(2-ethoxyethyl)-7-(5-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carboxylate

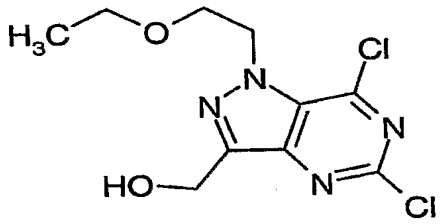


The title product was prepared by a method similar to that described for preparation 7 using the dichloro compound of preparation 6 and 2-amino-5-methylpyridine.

^{1}H NMR (DMSO-D_6, 400MHz) δ: 1.01 (t, 3H), 2.26 (s, 3H), 3.52 (m, 2H), 3.88 (m, 5H), 4.96 (m, 2H), 7.76 (m, 1H), 8.03 (m, 1H), 8.20 (m, 1H).
MS APCI+ m/z 391 $[MH]^+$

Preparation 9

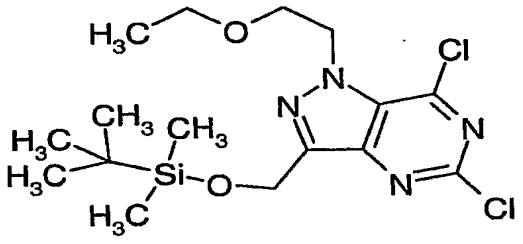
[5,7-Dichloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



The dichloro compound of preparation 6 (2.4g, 7.52mmol) was dissolved in tetrahydrofuran (60mL) and the reaction mixture cooled to -78°C. A 1M solution of diisobutylaluminium hydride in tetrahydrofuran (37.6mL, 37.6mmol) was added dropwise over 10 minutes and the reaction mixture stirred at -78°C for 10 minutes and then at -10°C for 1 hour. The reaction mixture was cooled to -78°C, quenched with ammonium chloride solution (25mL) and allowed to return to room temperature. The reaction mixture was diluted with dichloromethane (200mL) and water (100mL) and the solution filtered through Arbocel®, washing thourough with dichloromethane (3x100mL). The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to yield the title product, 1.67g.
^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.08 (t, 3H), 3.42 (m, 2H), 3.80 (m, 2H), 4.90 (m, 2H), 5.10 (s, 2H). MS APCI+ m/z 291 $[MH]^+$

Preparation 10

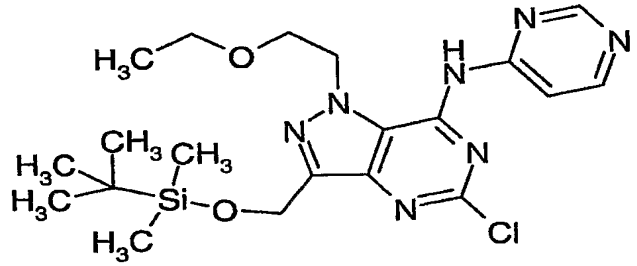
3-(*tert*-Butyldimethylsilyloxymethyl)-5,7-dichloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine



The alcohol of preparation 9 (1.32g, 4.53mmol) was dissolved in dichloromethane (25mL) and the solution treated with imidazole (339mg, 4.98mmol) and then *tert*-butyldimethylsilyl chloride (750mg, 4.98mmol). The reaction mixture was stirred at room temperature for 18 hours, diluted with dichloromethane (200mL) and washed with 10% potassium carbonate solution (100mL). The organic phase was dried over sodium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to yield the title product, 1.56g. ^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.00 (s, 6H), 0.78 (s, 9H), 0.93 (t, 3H), 3.29 (q, 2H), 3.71 (t, 2H), 4.72 (m, 2H), 4.94 (s, 2H). MS APCI+ m/z 405$[MH]^+$

Preparation 11

N-[3-(*tert*-Butyldimethylsilyloxymethyl)-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrimidin-4-ylamine



Pyrimidin-4-ylamine (1.10g, 11.55mmol) was dissolved in tetrahydrofuran (30mL) and the solution treated with sodium hexamethyldisilazide (2.12g, 11.55mmol) and stirred at room temperature for 20 minutes. The solution was treated with a solution of the dichloro compound of preparation 10 (1.56g, 3.85mmol) in tetrahydrofuran (10mL) and the reaction mixture stirred for 90 minutes at room

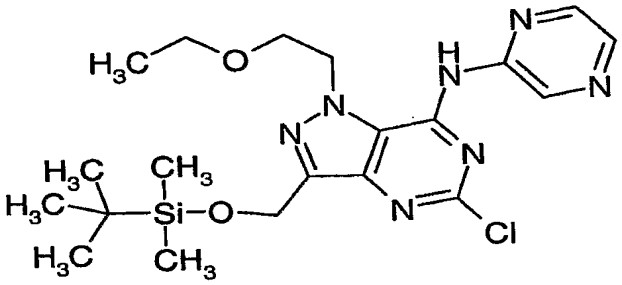
temperature. The reaction mixture was quenched with ammonium chloride solution (100mL) and extracted with dichloromethane (200mL). The organic phase was separated, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 97:3 to yield the title product, 830mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.00 (s, 6H), 0.77 (s, 9H), 1.08 (t, 3H), 3.54 (q, 2H), 3.80 (m, 2H), 4.63 (m, 2H), 4.90 (s, 2H), 8.33 (d, 1H), 8.51 (d, 1H), 8.77 (s, 1H).

MS APCI+ m/z 464 $[MH]^+$

Preparation 12

N-[3-(*tert*-Butyldimethylsilyloxymethyl)-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrazin-2-ylamine

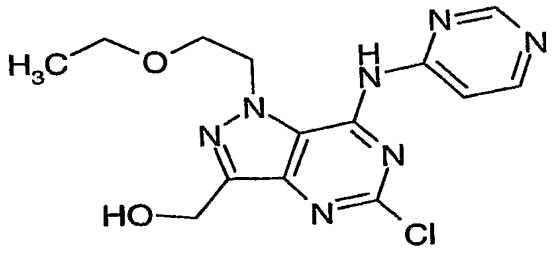


The title compound was prepared by a method similar to that described for preparation 11 using the dichloro compound of preparation 10 and aminopyrazine.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.18 (s, 6H), 0.93 (s, 9H), 1.21 (t, 3H), 3.65 (m, 2H), 3.97 (m, 2H), 4.80 (m, 2H), 5.06 (m, 2H), 8.30 (m, 2H), 9.77 (m, 1H), 10.17 (m, 1H)

Preparation 13

[5-Chloro-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



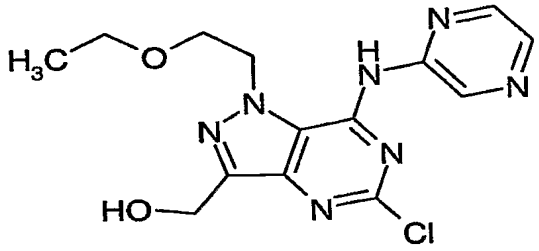
The protected alcohol of preparation 11 (2.0g, 1.76mmol) was dissolved in tetrahydrofuran (40mL) and the solution treated with a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (8.63mL, 8.63mmol). The reaction mixture was stirred for 90 minutes at room temperature and was then treated with additional tetrabutylammonium fluoride solution in tetrahydrofuran (4.32mL, 4.32mmol) and stirred for another hour. The reaction mixture was diluted with water (50mL) and the aqueous extracted with ethyl acetate (3x50mL). The combined organics were dried over magnesium sulphate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 99:1 to 95:5 to yield the title product, 1.25g.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.26 (t, 3H), 3.70 (q, 2H), 3.97 (m, 2H), 4.76 (m, 2H), 5.10 (s, 2H), 8.51 (d, 1H), 8.72 (d, 1H), 8.99 (s, 1H).

MS APCI+ m/z 350 $[MH]^+$

Preparation 14

[5-Chloro-1-(2-ethoxyethyl)-7-(pyrazin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol

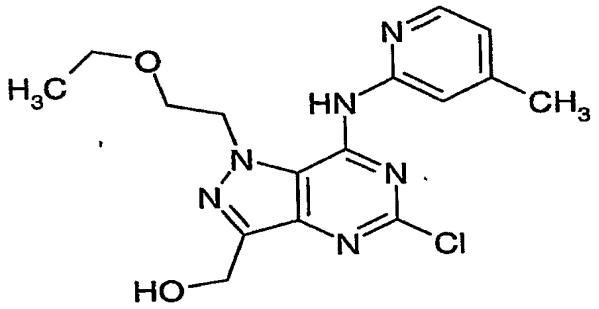


The title compound was prepared by a method similar to that described for preparation 13 using the protected alcohol of preparation 12.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.22 (t, 3H), 3.66 (m, 2H) 3.98 (m, 2H), 4.80 (m, 2H), 5.08 (s, 2H), 8.34 (m, 2H), 9.80 (m, 1H), 10.22 (m, 1H)

Preparation 15

[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



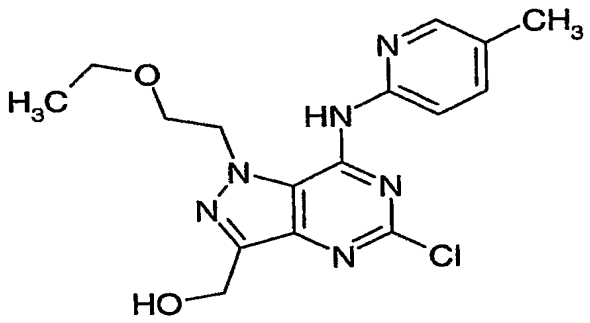
The ester of preparation 7 (1.89g, 4.84mmol) was suspended in tetrahydrofuran (450mL) and the reaction mixture cooled to -78°C. Diisobutylaluminium hydride (39mL, 1M solution in toluene, 39mmol) was added and the reaction mixture allowed to warm to -5°C. The reaction mixture was stirred at -5°C for 15 minutes before being re-cooled to -78°C and being quenched with aqueous ammonium chloride solution (10mL). The reaction mixture was allowed to warm to room temperature and partitioned between dichloromethane (200mL) and water (200mL). The mixture was filtered through Arbocel® and the organic layer separated, dried over magnesium sulphate and concentrated *in vacuo*. The crude product was triturated with ethyl acetate and the solid filtered off to yield the title product.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.11 (t, 3H), 2.46 (s, 3H), 3.61 (m, 2H), 3.94 (m, 2H), 4.86 (m, 2H), 5.07 (m, 2H), 6.96 (m, 1H), 8.19 (m, 1H), 8.48 (m, 1H)

MS APCI+ m/z 363 $[MH]^+$

Preparation 16

[5-Chloro-1-(2-ethoxyethyl)-7-(5-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol

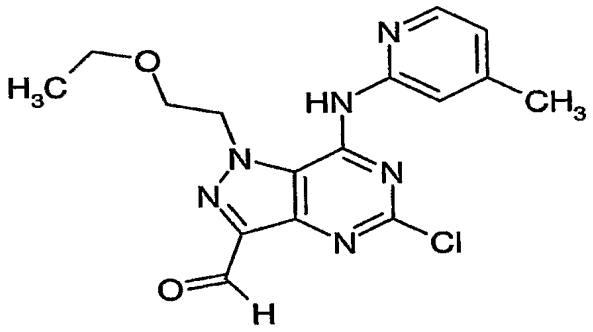


The title compound was prepared by a method similar to that described for preparation 15 using the ester of preparation 8.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.12 (t, 3H), 2.34 (s, 3H), 3.61 (q, 2H), 3.89 (m, 2H), 4.69 (m, 2H), 4.77 (s, 2H), 7.63 (d, 1H), 8.15 (s, 1H), 8.36 (d, 1H)

Preparation 17

5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbaldehyde



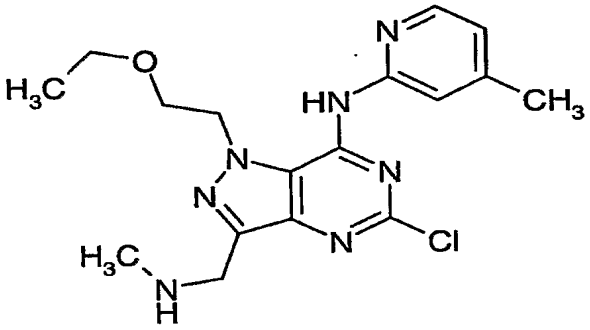
The alcohol of preparation 15 (90mg, 0.25mmol) was dissolved in dichloromethane (15.5mL) and the solution cooled to 0°C and treated with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (112mg, 0.93mmol). The reaction mixture was stirred at room temperature for 2 hours and was then treated with saturated sodium thiosulphate solution (13mL), sodium hydrogencarbonate solution (13mL) and ether (13mL). The mixture was allowed to stand for 15 minutes before being extracted into dichloromethane (3x100mL). The organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel

eluting with dichloromethane:methanol 100:0 to 98:2 to yield the title product, 53mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.10 (m, 3H), 2.40 (s, 3H), 3.62 (m, 2H), 3.99 (t, 2H), 4.85 (m, 2H), 6.90 (d, 1H), 8.20 (d, 1H), 8.40 (m, 1H), 10.35 (m, 1H)

Preparation 18

N-[5-Chloro-1-(2-ethoxyethyl)-3-methylaminomethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]-4-methylpyridin-2-ylamine



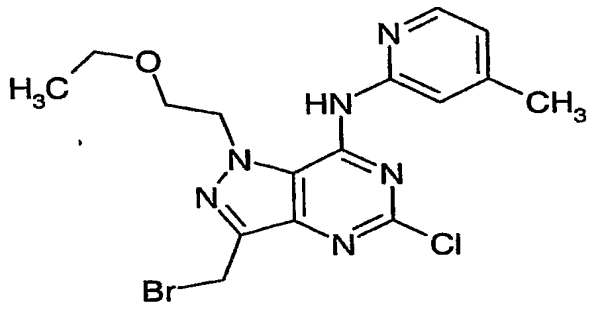
The aldehyde of preparation 17 (53mg, 0.15mmol) was dissolved in dichloromethane (2mL) and the solution treated with methylamine hydrochloride (11mg, 0.17mmol) and triethylamine (22μL, 0.17mmol). The mixture was stirred at room temperature for 30 minutes and was then treated with additional methylamine hydrochloride (11mg, 0.17mmol) and triethylamine (22μL, 0.17mmol) and stirred for a further 30 minutes. Sodium triacetoxyborohydride (48mg, 0.22mmol) was added to the mixture and the reaction mixture stirred for 18 hours at room temperature. The reaction mixture was concentrated *in vacuo* and the residue partitioned between sodium hydrogencarbonate solution (100mL) and dichloromethane (100mL). The aqueous was extracted with dichloromethane (3x10mL) and the organics combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia 95:5:0 to 90:10:1 to yield the title product, 19mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.10 (t, 3H), 2.37 (s, 3H), 2.72 (s, 3H), 3.58 (q, 2H), 3.90 (t, 2H), 4.38 (s, 2H), 4.85 (t, 2H), 6.81 (s, 1H), 8.10 (d, 1H), 8.30 (d, 1H)

MS APCI+ m/z 376 $[MH]^+$

Preparation 19

N-[3-Bromomethyl-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]-4-methylpyridin-2-ylamine



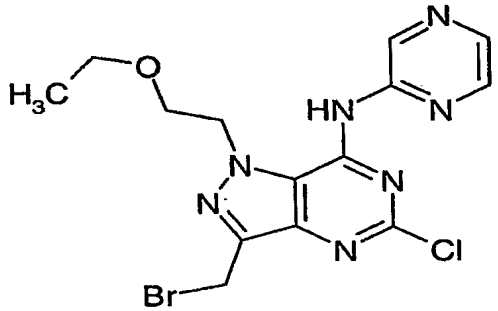
The alcohol of preparation 15 (560mg, 1.54mmol) was dissolved in dichloromethane (15mL) and the solution treated with tetrabromomethane (614mg, 1.85mmol) and cooled to 0°C in an ice bath. The mixture was treated dropwise with a solution of triphenylphosphine (567mg, 2.16mmol) in dichloromethane (5mL) and the reaction stirred at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 98:2 to yield the title product, 457mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.13 (t, 3H), 2.49 (s, 3H), 3.63 (q, 2H), 3.94 (t, 2H), 4.81 (s, 2H), 4.98 (t, 2H), 6.95 (s, 1H), 8.18 (d, 1H), 8.50 (d, 1H).

MS ES+ m/z 425 $[MH]^+$

Preparation 20

N-[3-Bromomethyl-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrazin-2-ylamine

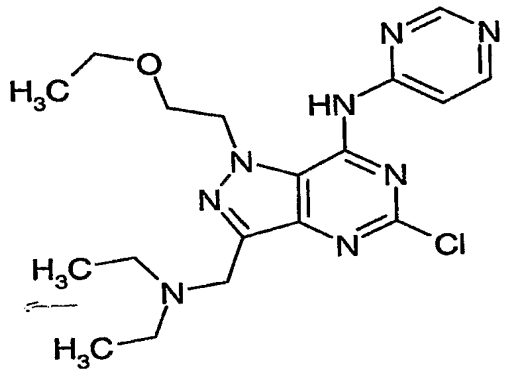


The title compound was prepared by a method similar to that described for preparation 19 using the alcohol of preparation 14.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.12 (t, 3H), 3.64 (q, 2H), 3.94 (t, 2H), 4.81 (s, 2H), 4.98 (t, 2H), 6.95 (s, 1H), 8.16 (d, 1H), 8.46 (d, 1H)

Preparation 21

N-[5-Chloro-3-(diethylaminomethyl)-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrimidin-4-ylamine



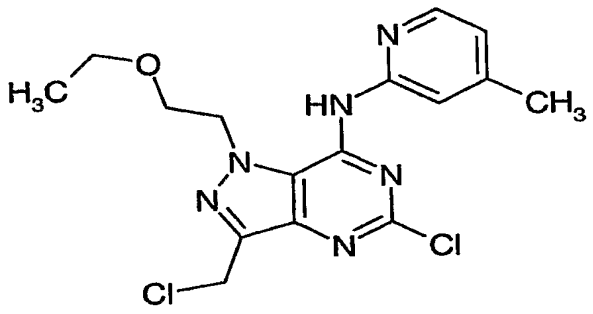
The alcohol of preparation 13 (446mg, 1.28mmol) was dissolved in dichloromethane (30mL) and the solution treated with tetrabromomethane (507mg, 1.53mmol) and triphenylphosphine (401mg, 1.53mmol). The reaction mixture was stirred at room temperature for 2 hours, additional tetrabromomethane (85mg, 0.26mmol) and triphenylphosphine (67mg, 0.26mmol) were added and the reaction mixture stirred for a further 2 hours. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with pentane:ethyl acetate 80:20. The crude product was further purified by column chromatography on silica gel once more, eluting with toluene:diethylamine 95:5 to yield the title product, 196mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.19 (t, 3H), 1.14 (t, 6H), 2.99 (m, 4H), 3.67 (q, 2H), 3.96 (t, 2H), 4.57 (s, 2H), 4.79 (t, 2H), 8.41 (d, 1H), 8.67 (d, 1H), 8.99 (s, 1H)

MS ES+ m/z 405 $[MH]^+$

Preparation 22

N-[5-Chloro-3-chloromethyl-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]-4-methylpyridin-2-ylamine



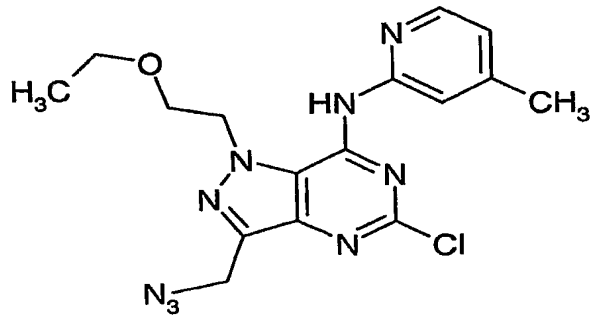
The alcohol of preparation 15 (1.80g, 5.00mmol) was dissolved in dichloromethane (15mL) and the solution treated with thionyl chloride (1.50mL, 17mmol). The reaction mixture was stirred at room temperature for 18 hours and concentrated *in vacuo*, the residue was azeotroped with toluene and then dried *in vacuo*. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 95:5 to yield the title product, 980mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.92 (t, 3H), 2.63 (s, 3H), 3.58 (m, 2H), 3.91 (m, 2H), 4.81 (s, 2H), 5.20 (m, 2H), 7.14 (m, 1H), 8.16 (m, 1H), 8.97 (m, 1H)

MS APCI+ m/z 381 $[MH]^+$

Preparation 23

N-[3-Azidomethyl-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]-4-methylpyridin-2-ylamine



The chloro compound of preparation 22 (700mg, 1.80mmol) was dissolved in N,N-dimethylformamide (10mL) and the solution treated with sodium azide (129mg, 1.98mmol). The reaction mixture was stirred at room temperature for 1

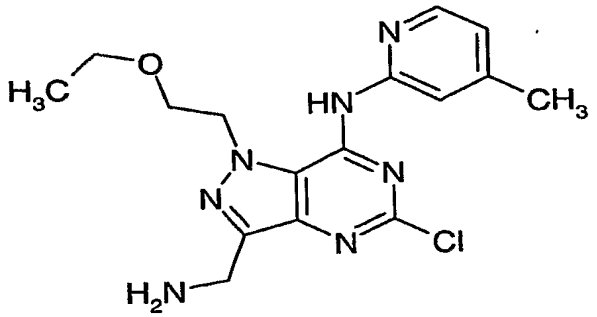
hour and then allowed to stand at room temperature for a further 18 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in water (100mL) and washed with ether (4x20mL). The ether washings were combined, washed with water (20mL), dried over magnesium sulphate and concentrated *in vacuo* to yield the title product, 600mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.20 (t, 3H), 2.40 (s, 3H), 3.60 (q, 2H), 3.95 (t, 2H), 4.70 (s, 2H), 4.80 (m, 2H), 6.90 (s, 1H), 8.20 (s, 1H), 8.30 (s, 1H), 10.00 (s, 1H)

MS APCI+ m/z 388 $[MH]^+$

Preparation 24

N-[3-Aminomethyl-5-chloro-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]-4-methylpyridin-2-ylamine

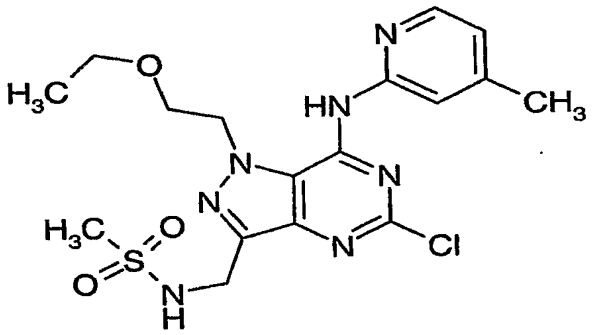


The azide of preparation 23 (130mg, 0.34mmol) was dissolved in tetrahydrofuran (5mL) and the solution treated with triphenylphosphine (92mg, 0.35mmol). The reaction mixture was stirred at room temperature for 2 hours, diluted with water (5mL), and stirred for a further 18 hours. The reaction mixture was concentrated *in vacuo* and the residue taken up in brine and extracted with dichloromethane. The dichloromethane phase was dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonium hydroxide 95:5:0.5 to yield the title product, 70mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.23 (t, 3H), 2.45 (s, 3H), 3.65 (q, 2H), 3.95 (t, 2H), 4.20 (s, 2H), 4.78 (t, 2H), 6.82 (s, 1H), 8.18 (m, 1H), 8.30 (m, 1H). MS APCI+ m/z 362 $[MH]^+$

Preparation 25

N-[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]methanesulfonamide



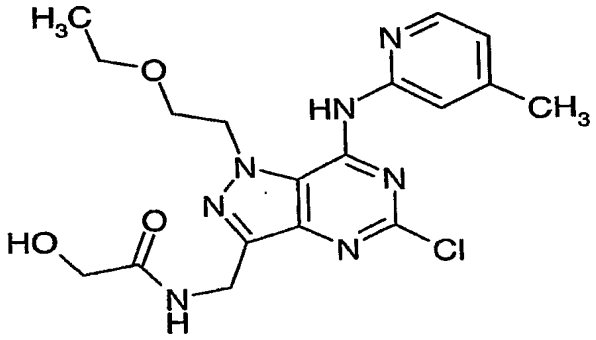
The amine of preparation 24 (150mg, 0.40mmol) was dissolved in dichloromethane (5mL) and the solution treated with N-ethyldiisopropylamine (108μL, 0.62mmol) and methanesulfonyl chloride (34μL, 0.44mmol). The reaction mixture was stirred at room temperature for 18 hours before being concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 98:2 to yield the title product, 110mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 2.40 (s, 3H), 3.00 (s, 3H), 3.60 (q, 2H), 3.90 (t, 2H), 4.50 (s, 2H), 4.70 (t, 2H), 6.90 (d, 1H), 8.15 (d, 1H), 8.40 (s, 1H).

MS APCI+ m/z 438 $[M-H]^-$

Preparation 26

N-[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-2-hydroxyacetamide

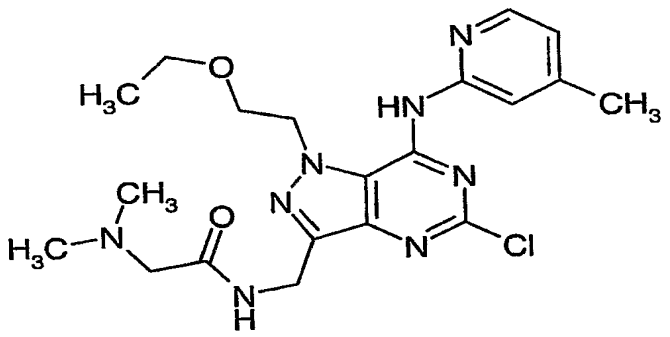


The amine of preparation 24 (50mg, 0.14mmol) was dissolved in dichloromethane (5mL) and the solution treated with glycolic acid (11mg, 0.14mmol), N-ethyldiisopropylamine (36μL, 0.21mmol) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (57mg, 0.15mmol). The reaction mixture was then stirred at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (20mL), washed with water (10mL), dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 98:2 to yield the title product, 50mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.20 (t, 3H), 2.40 (s, 3H), 3.60 (m, 2H), 3.90 (t, 2H), 4.20 (s, 2H), 4.75 (m, 2H), 4.80 (d, 2H), 6.85 (m, 1H), 7.60 (m, 1H), 8.20 (m, 1H), 8.30 (m, 1H), 10.10 (m, 1H). MS APCI+ m/z 420 $[MH]^+$

Preparation 27

N-[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-2-(dimethylamino)acetamide

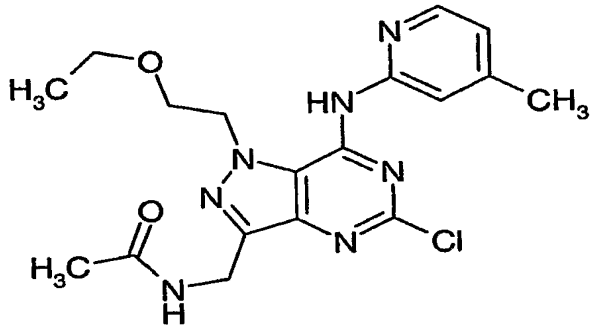


The title product was prepared by a method similar to that described for preparation 26 using N,N-dimethylaminoacetic acid and the amine of preparation 24. The crude product was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonium hydroxide 98:2:0.5.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.20 (t, 3H), 2.39 (s, 6H), 2.40 (s, 3H), 3.10 (s, 2H), 3.60 (q, 2H), 3.90 (t, 2H), 4.75 (m, 2H), 4.80 (d, 2H), 6.85 (m, 1H), 7.90 (m, 1H), 8.20 (m, 1H), 8.35 (m, 1H), 10.00 (m, 1H). MS APCI+ m/z 447 $[MH]^+$

Preparation 28

N-[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide

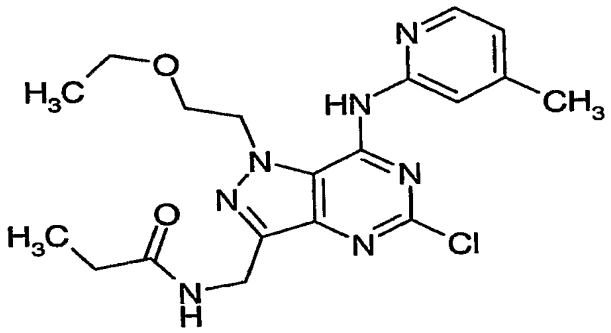


The amine of preparation 24 (70mg, 0.19mmol) was dissolved in dichloromethane (5mL) and the solution treated with acetyl chloride (16µL, 0.23mmol) and N-ethyldiisopropylamine (40µL, 0.23mmol). The reaction mixture was stirred at room temperature for 1 hour and then concentrated *in vacuo*. The residue was taken up in methanol and treated dropwise with dichloromethane until all solid was in solution. The solution was treated with 2M sodium hydroxide solution (500µL) and then stirred at room temperature for 30 minutes. The solution was concentrated *in vacuo* and the residue taken up in water (5mL) and washed with dichloromethane (3x10mL). The organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 98:2 to yield the title product, 50mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.18 (t, 3H), 2.20 (s, 3H), 2.40 (s, 3H), 3.65 (q, 2H), 3.95 (t, 2H), 4.75 (m, 2H), 4.80 (t, 2H), 6.50 (m, 1H), 6.85 (m, 1H), 8.20 (m, 1H), 8.30 (s, 1H), 10.00 (s, 1H). MS APCI+ m/z 404 $[MH]^+$

Preparation 29

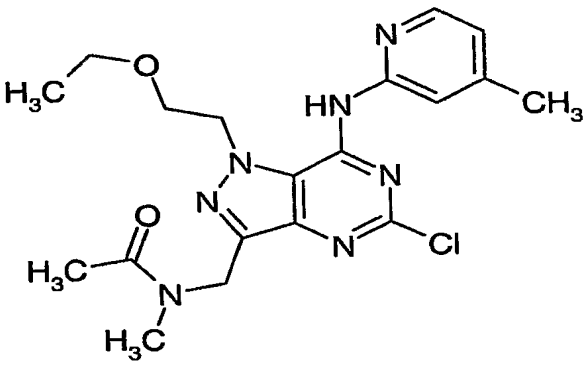
N-[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]propionamide



The title product was prepared by a method similar to that described for preparation 28 using propionyl chloride and the amine of preparation 24.
^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.20 (t, 6H), 2.30 (m, 2H), 2.40 (s, 3H), 3.60 (q, 2H), 3.90 (t, 2H), 4.75 (t, 2H), 4.80 (d, 2H), 6.60 (m, 1H), 6.90 (d, 1H), 8.20 (d, 1H), 8.30 (s, 1H), 10.10 (s, 1H). MS ES+ m/z 418 $[MH]^+$

Preparation 30

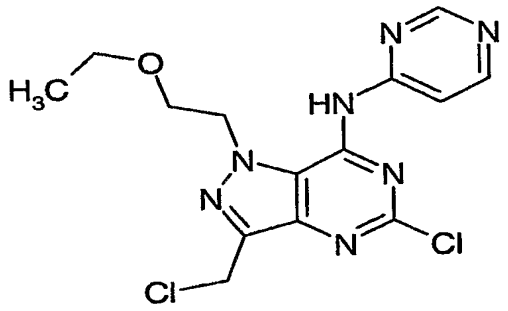
N-[5-Chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-methylacetamide



The title product was prepared by a method similar to that described for preparation 28 using the amine of preparation 18 and acetyl chloride.
^{1}H NMR ($CDCl_3$, 400MHz) δ: Rotamers 1.20 (t, 3H), 2.15 (m, 1H), 2.40 (s, 2H), 2.45 (s, 3H), 3.05, 3.15 (2xs, 3H), 3.65 (q, 2H), 4.70 (t, 2H), 4.80 (m, 3H), 4.90 (s, 1H), 6.85 (t, 1H), 8.20 (m, 1H), 8.30 (s, 1H), 10.00 (s, 1H).
MS ES+ m/z 418 $[MH]^+$

Preparation 31

N-[5-Chloro-3-chloromethyl-1-(2-ethoxyethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrimidin-4-ylamine

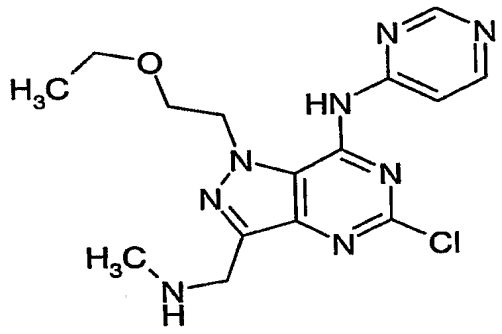


The alcohol of preparation 13 (1.35g, 3.86mmol) was dissolved in dichloromethane (10mL) and the solution treated dropwise with thionyl chloride (1.13mL, 15.44mmol). The reaction mixture was stirred at room temperature for 18 hours and then concentrated *in vacuo*. The residue was azeotroped with toluene to yield the title product, 1.44g.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.24 (t, 3H), 3.72 (q, 2H), 4.00 (t, 2H), 4.90 (t, 2H), 4.99 (s, 2H), 8.68 (m, 1H), 8.86 (m, 1H), 9.22 (m, 1H). MS APCI+ m/z 368 $[MH]^+$

Preparation 32

N-[5-Chloro-1-(2-ethoxyethyl)-3-methylaminomethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrimidin-4-ylamine



The chloro compound of preparation 31 (770mg, 2.09mmol) and N-ethyldiisopropylamine (400μL, 2.30mmol) were dissolved in N,N-dimethylformamide (10mL) and the solution treated with a 33% solution of methylamine in ethanol (6mL, 42.0mmol). The reaction mixture was stirred at room temperature for 3 hours and then concentrated *in vacuo*. The residue was

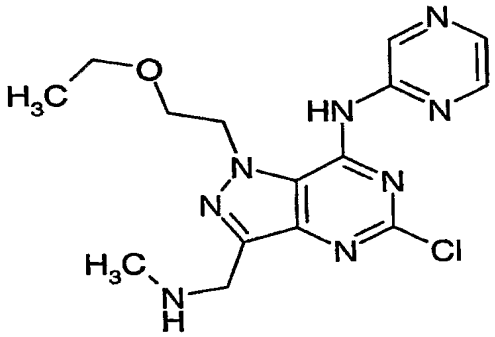
purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia 95:5:0 to 95:5:0.5 to 90:10:1 to yield the title product, 560mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.17 (t, 3H), 2.52 (s, 3H), 3.65 (q, 2H), 3.95 (t, 2H), 4.13 (s, 2H), 4.87 (m, 2H), 8.36 (dd, 1H), 8.65 (d, 1H), 8.84 (s, 1H)

MS APCI+ m/z 363 $[MH]^+$

Preparation 33

N-[5-Chloro-1-(2-ethoxyethyl)-3-methylaminomethyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-7-yl]pyrazin-2-ylamine

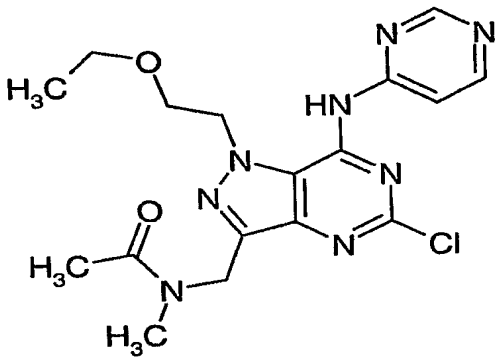


The bromo compound of preparation 20 (109mg, 0.26mmol) and a 33% solution of methylamine in ethanol (490µL, 5.2mmol) were added to 1-methyl-2-pyrrolidinone (1mL) and the reaction mixture heated to 35°C for 1 hour. The reaction mixture was concentrated *in vacuo* to yield the title product.

MS APCI+ m/z 363 $[MH]^+$

Preparation 34

N-[5-Chloro-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-methylacetamide

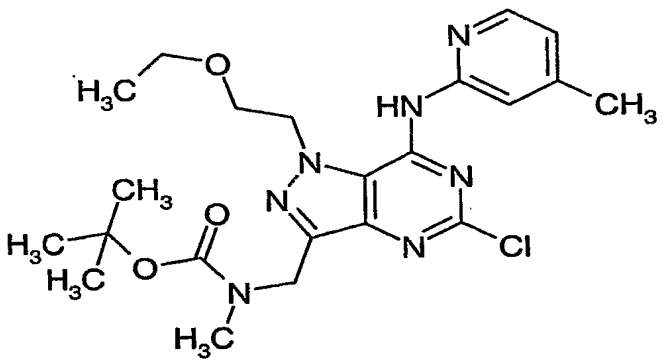


The amine of preparation 32 (530mg, 1.45mmol) and N-ethyldiisopropylamine (280μL, 1.59mmol) were dissolved in dichloromethane (15mL) and the solution treated with acetyl chloride (114μL, 1.59mmol). The reaction mixture was stirred at room temperature for 45 minutes and then concentrated *in vacuo*. The residue was dissolved in methanol (15mL), treated with 2M sodium hydroxide solution (5mL) and allowed to stand at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 96:4 to yield the title product, 495mg.

^{1}H NMR (CD_3OD, 400MHz) δ: Rotamers 1.20 (t, 3H), 2.16, 2.38 (2xs, 3H), 2.99, 3.18 (2xs, 3H), 3.67 (m, 2H), 3.95 (q, 2H), 4.75-4.91 (m, 4H), 8.43 (d, 1H), 8.67 (dd, 1H), 8.86 (s, 1H). MS APCI+ m/z 405 $[MH]^+$

Preparation 35

tert-Butyl *N*-[5-chloro-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-methylcarbamate

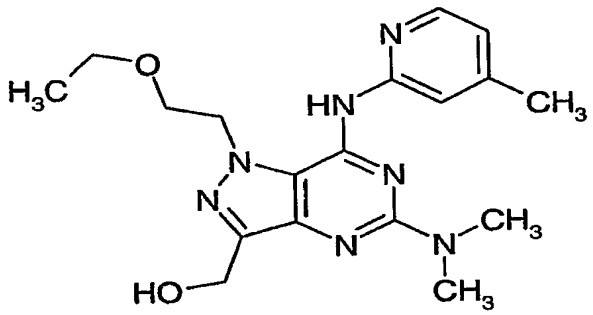


The amine of preparation 18 (157mg, 0.42mmol) was dissolved in dichloromethane (10mL) and the solution treated with di-*tert*-butyldicarbonate (129mg, 0.59mmol). The reaction mixture stirred at room temperature for 1 hour and concentrated *in vacuo* to yield the title product, 200mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 1.52 (s, 9H), 2.42 (s, 3H), 2.96 (s, 3H), 3.60 (q, 2H), 3.94 (t, 2H), 4.75 (s, 2H), 4.82 (t, 2H), 7.00 (d, 1H), 8.18 (m, 1H), 8.36 (m, 1H). MS APCI+ m/z 476 $[MH]^+$

Preparation 36

[5-Dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



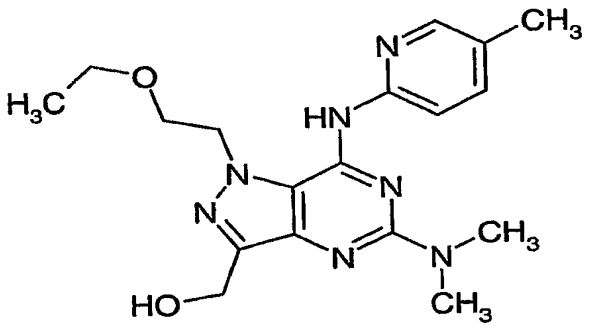
The chloro compound of preparation 15 (780mg, 2.15mmol) and N-ethyldiisopropylamine (1.125mL, 6.46mmol) were dissolved in dimethyl sulphoxide (6mL) and the mixture treated with a 5.6M solution of dimethylamine in ethanol (1.15mL, 6.46mmol) and heated to 120°C for 18 hours in a sealed vessel. The reaction mixture was partitioned between dichloromethane (100mL) and water (100mL) and the organic phase separated and washed with water (3x200mL). The organic phase was dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 98:2. The product was triturated with ether to yield the title product, 230mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.07 (t, 3H), 2.38 (s, 3H), 3.20 (s, 6H), 3.60 (q, 2H), 3.85 (t, 2H), 4,65 (t, 2H), 4.80 (s, 2H), 6.90 (d, 1H), 8.12 (d, 1H), 8.39 (s, 1H)

MS APCI+ m/z 372 $[MH]^+$

Preparation 37

[5-Dimethylamino-1-(2-ethoxyethyl)-7-(5-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



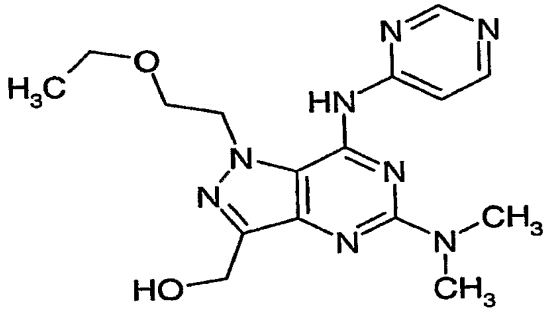
The title product was prepared by a method similar to that described for preparation 36 using the chloro compound of preparation 16.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.12 (t, 3H), 2.33 (s, 3H), 3.20 (s, 6H), 3.59 (q, 2H), 3.85 (m, 2H), 4.71 (m, 2H), 4.81 (s, 2H), 7.62 (d, 1H), 8.13 (s, 1H), 8.38 (d, 1H)

MS APCI+ m/z 372 $[MH]^+$

Preparation 38

[5-Dimethylamino-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-yl]methanol



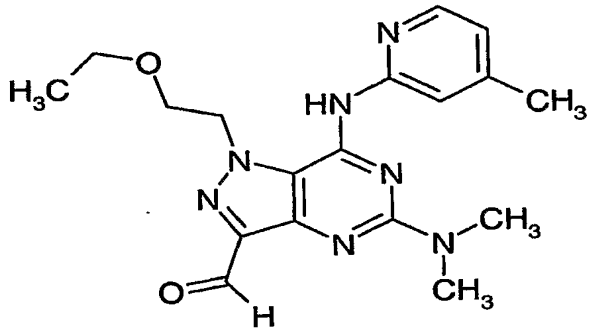
The title product was prepared by a method similar to that described for preparation 36 using the chloro compound of preparation 1.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.21 (t, 3H), 3.30 (s, 6H), 3.66 (q, 2H), 3.92 (t, 2H), 4.69 (t, 2H), 4.83 (s, 2H), 8.39 (d, 1H), 8.58 (d, 1H), 8.79 (s, 1H)

MS APCI+ m/z 359 $[MH]^+$

Preparation 39

5-Dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbaldehyde

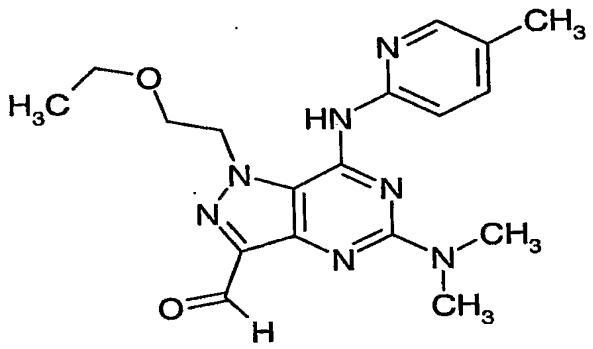


The alcohol of preparation 36 (330mg, 0.89mmol) was dissolved in dichloromethane (15.5mL) and the solution cooled to 0°C and treated with 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (394mg, 0.93mmol). The reaction mixture was stirred at room temperature for 2 hours and was then treated with saturated sodium thiosulphate solution (13mL), sodium hydrogencarbonate solution (13mL) and ether (13mL). The mixture was allowed to stand for 15 minutes before being extracted into dichloromethane (3x100mL). The organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 98:2 to yield the title product, 300mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.10 (m, 3H), 2.40 (s, 3H), 3.30 (s, 6H), 3.62 (m, 2H), 3.99 (t, 2H), 4.85 (m, 2H), 6.90 (d, 1H), 8.20 (d, 1H), 8.40 (m, 1H), 10.35 (s, 1H). MS APCI+ m/z 370 $[MH]^+$

Preparation 40

5-Dimethylamino-1-(2-ethoxyethyl)-7-(5-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbaldehyde



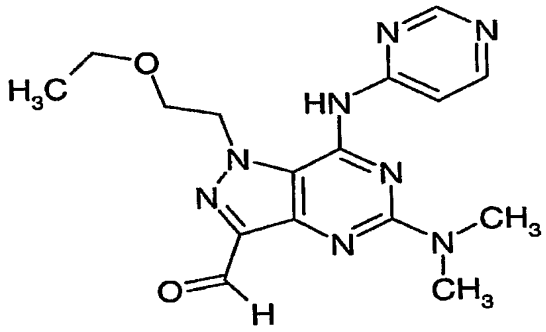
The title product was prepared by a method similar to that described for preparation 39 using the alcohol of preparation 37.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.11 (t, 3H), 2.34 (s, 3H), 3.24 (s, 6H), 3.61 (q, 2H), 3.97 (m, 2H), 4.80 (m, 2H), 7.63 (d, 1H), 8.13 (s, 1H), 8.31 (d, 1H), 10.10 (s, 1H).

MS APCI+ m/z 370 $[MH]^+$

Preparation 41

5-Dimethylamino-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidine-3-carbaldehyde

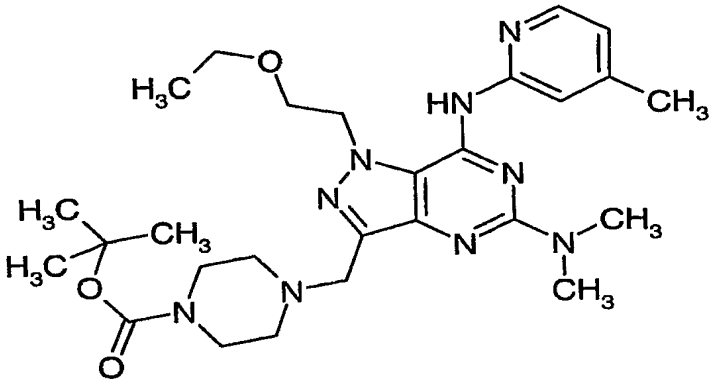


The title product was prepared by a method similar to that described for preparation 39 using the alcohol of preparation 38.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.21 (t, 3H), 3.25 (s, 6H), 3.62 (q, 2H), 4.00 (t, 2H), 4.83 (t, 2H), 8.35 (d, 1H), 8.59 (d, 1H), 8.82 (s, 1H). MS APCI+ m/z 357 $[MH]^+$

Preparation 42

tert-Butyl 4-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]piperazine-1-carboxylate



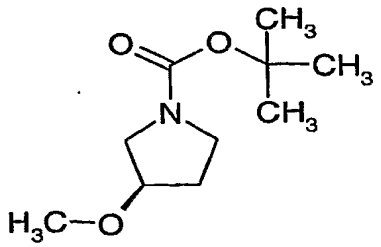
The aldehyde of preparation 39 (75mg, 0.20mmol) was dissolved in dichloromethane (5mL) and the solution treated with sodium triacetoxyborohydride (52mg, 0.24mmol) and piperazine-1-carboxylic acid *tert*-butyl ester (45mg, 0.24mmol) The reaction mixture was shaken in a ReactiVial™ for 2 hours at room temperature and then treated with saturated sodium bicarbonate solution (8mL). The mixture was extracted into dichloromethane (3x15mL) and the organics combined and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 97.5:2.5 to yield the title product, 80mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 1.42 (s, 9H), 2.38 (s, 3H), 2.59 (m, 4H), 3.20 (s, 6H), 3.40 (m, 4H), 3.58 (q, 2H), 3.80 (s, 2H), 3.81 (t, 2H), 4.65 (m, 2H), 4.85 (d, 1H), 6.88 (d, 1H), 8.10 (d, 1H), 8.40 (s, 1H).

MS APCI+ m/z 538 $[MH]^+$

Preparation 43

tert-Butyl (3*R*)-3-methoxypyrrolidine-1-carboxylate

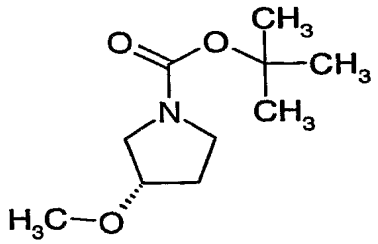


(3*R*)-3-Hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12.5g, 66.70mmol) was dissolved in tetrahydrofuran (334mL) and the reaction mixture cooled to 0°C in an ice bath. The reaction mixture was treated with 80% sodium hydride in mineral oil (2.20g, 73.3mmol) and stirred until back at room temperature. The reaction mixture was then treated with methyl iodide (14.5g, 100.0mmol) and stirred at room temperature for 18 hours. The reaction mixture was diluted with water (100mL) and concentrated *in vacuo* until just the aqueous remained. The aqueous solution was extracted with ethyl acetate (750mL), the organic layer separated, dried over magnesium sulphate and concentrated *in vacuo* to yield the title product as a brown oil, 12.48g.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.41 (s, 9H), 1.95 (m, 2H), 3.30 (s, 3H), 3.40 (m, 4H), 3.86 (m, 1H)

Preparation 44

tert-Butyl (3*S*)-3-methoxypyrrolidine-1-carboxylate

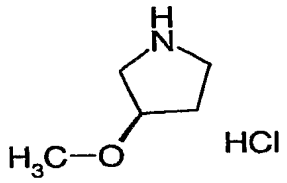


The title product was prepared by a method similar to that described for preparation 43 using (3*S*)-3-hydroxy-pyrrolidine-1-carboxylic acid *tert*-butyl ester.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.41 (s, 9H), 1.95 (m, 2H), 3.30 (s, 3H), 3.40 (m, 4H), 3.86 (m, 1H)

Preparation 45

(3*R*)-3-Methoxypyrrolidine hydrochloride



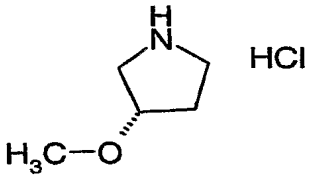
Hydrogen chloride gas was bubbled through an ice-cooled solution of the compound from preparation 43 (6.02g, 30.0mmol) in dichloromethane (30mL),

and the reaction then allowed to warm to room temperature and stirred for 48 hours. The solution was concentrated under reduced pressure and the residue triturated with ether. The resulting crystals were filtered off and dried *in vacuo* to afford the title compound.

^{1}H NMR (CD_3OD, 400MHz) δ: 2.06 (m, 1H), 2.20 (m, 1H), 3.26-3.42 (m, 7H), 4.17 (m, 1H).

Preparation 46

(3*S*)-3-Methoxypyrrolidine hydrochloride

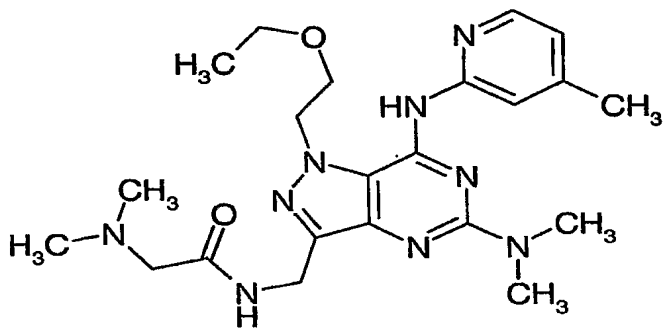


The title compound was obtained from the compound from preparation 44, following a similar method to that described in preparation 45.

^{1}H NMR (CD_3OD, 400MHz) δ: 2.14 (m, 1H), 2.20 (m, 1H), 3.24-3.44 (m, 7H), 4.18 (m, 1H).

Example 1

2-Dimethylamino-*N*-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide



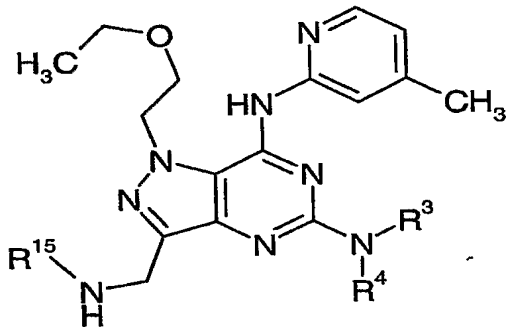
The chloro compound of preparation 27 (50mg, 0.11mmol) was dissolved in dimethyl sulphoxide (2mL) and the solution treated with N-ethyldiisopropylamine (22μL, 0.12mmol) and a 33% solution of dimethylamine in ethanol (160μL, 1.10mmol). The reaction mixture was heated to 100°C in a ReactiVial™ for 18

hours and then partitioned between water (20mL) and ethyl acetate (20mL) and the aqueous washed with ethyl acetate (2x20mL). The organics were combined, washed with water (10mL), dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonium hydroxide 98:2:0.5 to yield the title product 32mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 2.30 (s, 6H), 2.40 (s, 3H), 3.00 (s, 2H), 3.25 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H), 4.70 (m, 4H), 6.90 (d, 1H), 8.10 (d, 1H), 8.40 (s, 1H). MS APCI+ m/z 456 $[MH]^+$

Examples 2 - 15

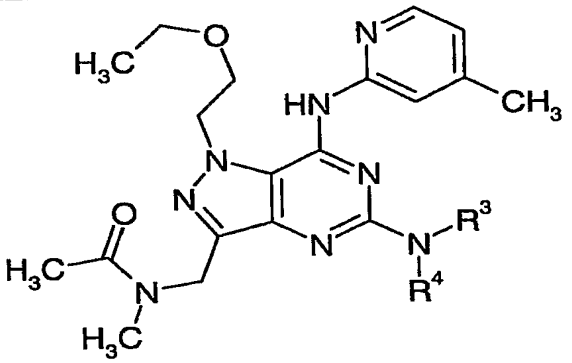
The following compounds, of the general formula shown below, were prepared by a method similar to that described for example 1 using the appropriate chloro compound of preparations 18, 25, 26, 28, 29 and 30, and the appropriate HNR^3R^4 amine.



No.	$-NR^3R^4$	R^{15}	Data
2	$-N(CH_3)_2$	CH_3SO_2-	^{1}H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 2.40 (s, 3H), 3.00 (s, 3H), 3.20 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H), 4.50 (s, 2H), 4.70 (t, 2H), 6.90 (d, 1H), 8.15 (d, 1H), 8.40 (s, 1H). MS APCI+ m/z 449 $[MH]^+$

3	$-NHCH_2CH_3$	CH_3SO_2-	^1H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 1.30 (t, 3H), 2.40 (s, 3H), 2.90 (s, 3H), 3.50 (q, 2H), 3.60 (q, 2H), 3.90 (t, 2H), 4.50 (s, 2H), 4.70 (m, 1H), 4.85 (m, 2H), 6.90 (d, 1H), 8.10 (d, 1H). MS APCI+ m/z 449 $[MH]^+$
4	$-N(CH_3)_2$	$HOCH_2C(O)-$	^1H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 2.40 (s, 3H), 3.20 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H), 4.05 (s, 2H), 4.70 (m, 4H), 6.90 (m, 1H), 8.15 (d, 1H), 8.40 (s, 1H). MS APCI+ m/z 429 $[MH]^+$
5	$-NHCH_2CH_3$	$HOCH_2C(O)-$	^1H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 1.30 (t, 3H), 2.40 (s, 3H), 3.50 (q, 2H), 3.60 (q, 2H), 3.85 (t, 2H), 4.00 (s, 2H), 4.60 (s, 4H), 6.90 (s, 1H), 8.15 (d, 1H), 8.45 (s, 1H). MS ES+ m/z 429 $[MH]^+$
6	$-N(CH_3)_2$	$CH_3C(O)-$	^1H NMR (CD_3OD, 400MHz) δ: 1.20 (t, 3H), 2.10 (s, 3H), 2.40 (s, 3H), 3.20 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H) 4.60 (t, 2H), 4.80 (d, 2H), 6.80 (d, 1H), 7.50 (m, 1H), 8.20 (s, 1H), 8.35 (s, 1H), 9.70 (s, 1H). MS ES+ m/z 413 $[MH]^+$
7	$-NHCH_3$	$CH_3C(O)-$	^1H NMR (CD_3OD, 400MHz) δ: 1.20 (t, 3H), 2.10 (s, 3H), 2.40 (s, 3H), 3.10 (s, 3H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60 (t, 2H), 4.70 (d, 2H), 4.90 (m, 1H), 6.80 (d, 1H), 7.30 (m, 1H), 8.18 (d, 1H), 8.30 (s, 1H), 9.75 (s, 1H). MS ES+ m/z 399.8 $[MH]^+$

8	$-NHCH_2CH_3$	$CH_3C(O)-$	^1H NMR (CD_3OD, 400MHz) δ: 1.20 (t, 3H), 1.30 (t, 3H), 2.10 (s, 3H), 2.40 (s, 3H), 3.50 (q, 2H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60 (t, 2H), 4.75 (d, 2H), 4.80 (m, 1H), 6.80 (d, 1H), 8.20 (d, 1H), 8.30 (s, 1H), 9.75 (s, 1H). MS ES+ m/z 413 $[MH]^+$
9	$-N(CH_3)_2$	$CH_3CH_2C(O)-$	^1H NMR (CD_3OD, 400MHz) δ: 1.19 (t, 3H), 1.20 (t, 3H), 2.30 (q, 2H), 2.40 (s, 3H), 3.20 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60 (t, 2H), 4.80 (d, 2H), 6.80 (d, 1H), 7.60 (m, 1H), 8.20 (d, 1H), 8.40 (s, 1H), 9.70 (m, 1H). MS ES+ m/z 427 $[MH]^+$
10	$-NHCH_3$	$CH_3CH_2C(O)-$	^1H NMR ($CDCl_3$, 400MHz) δ: 1.95 (t, 3H), 2.20 (t, 3H), 2.30 (q, 2H), 2.40 (s, 3H), 3.10 (d, 3H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60 (t, 2H), 4.75 (d, 2H), 4.80 (m, 1H), 6.80 (d, 1H), 7.30 (m, 1H), 8.20 (d, 1H), 8.30 (s, 1H), 9.75 (s, 1H). MS ES+ m/z 413 $[MH]^+$
11	$-NHCH_2CH_3$	$CH_3CH_2C(O)-$	^1H NMR ($CDCl_3$, 400MHz) δ: 1.03 (t, 3H), 1.20 (t, 3H), 1.30 (t, 3H), 2.30 (q, 2H), 2.40 (s, 3H), 3.50 (q, 2H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60 (t, 2H), 4.75 (d, 2H), 4.80 (t, 1H), 6.80 (d, 1H), 8.15 (d, 1H), 8.25 (s, 1H), 9.70 (s, 1H). MS ES+ m/z 427 $[MH]^+$
12	$-N(CH_3)_2$	CH_3-	^1H NMR ($CDCl_3$, 400MHz) δ: 1.20 (t, 3H), 2.38 (s, 3H), 2.72 (s, 3H), 3.22 (s, 6H), 3.63 (m, 2H), 3.91 (m, 2H), 4.43 (s, 2H), 4.68 (m, 2H), 6.83 (m, 1H), 8.18 (m, 1H). MS APCI+ m/z 385 $[MH]^+$

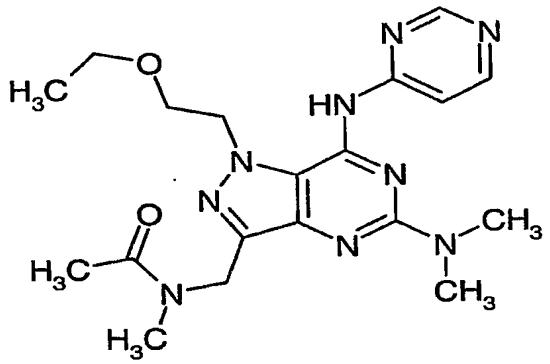


No.	-NR^3R^4	Data
13	-$N(CH_3)_2$	^{1}H NMR ($CDCl_3$, 400MHz) δ: Rotamers 1.20 (t, 3H), 2.15 (s, 0.5H), 2.40 (s, 3H), 2.50 (s, 2.5H), 3.00 (s, 2.5H), 3.10 (s, 0.5H), 3.20 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60 (s, 1.5H, t, 2H), 4.80 (s, 0.5H), 6.80 (t, 1H), 8.20 (d, 1H), 8.35 (s, 1H), 9.60 (s, 1H). MS ES+ m/z 427 $[MH]^+$
14	-$NHCH_3$	^{1}H NMR ($CDCl_3$, 400MHz) δ: Rotamers 1.20 (t, 3H), 2.15 (s, 1H), 2.40 (s, 3H), 2.50 (s, 2H), 3.10 (s, 6H), 3.60 (q, 2H), 3.90 (t, 2H), 4.65 (t, 2H), 4.75, 4.85 (2xs, 2H), 4.90 (q, 1H), 6.80 (d, 1H), 8.15 (d, 1H), 8.25, 8.30 (2xs, 1H), 9.65, 9.70 (2xs, 1H). MS ES+ m/z 413 $[MH]^+$
15	-$NHCH_2CH_3$	^{1}H NMR ($CDCl_3$, 400MHz) δ: Rotamers 1.20 (t, 3H), 1.25 (t, 3H), 2.10, 2.45 (2xs, 3H), 2.40 (s, 3H), 3.00, 3.10 (2xs, 3H), 3.50 (q, 2H), 3.60 (q, 2H), 3.90 (t, 2H), 4.60, 4.85 (2xs, 4H), 4.80 (m, 1H), 6.80 (s, 1H), 8.20 (d, 1H), 8.25, 8.30 (2xs 1H), 9.60, 9.65 (2xs, 1H). MS ES+ m/z 427 $[MH]^+$

- Examples 3, 5, 8, 11 and 15 used a 2M solution of ethylamine in methanol as the source of the HNR^3R^4 amine
- Examples 2, 4, 6, 9, 12 and 13 used 33% solutions of dimethylamine in ethanol as the source of the HNR^3R^4 amine
- Examples 7, 10 and 14 used 2M solutions of methylamine in methanol as the HNR^3R^4 amine

Example 16

N-[5-Dimethylamino-1-(2-ethoxyethyl)-7-(pyrimidin-4-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-methylacetamide



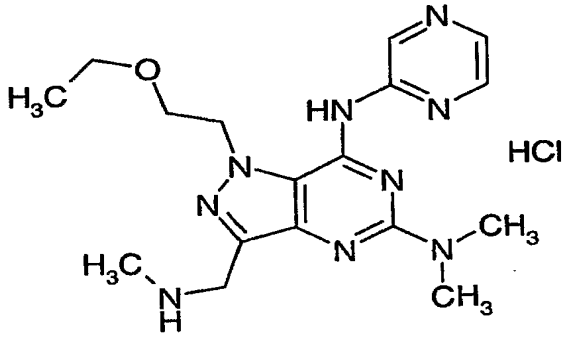
The title product was prepared by a method similar to that described for example 1 using the chloro compound of preparation 34 and a 33% solution of dimethylamine in ethanol.

^{1}H NMR (CD_3OD, 400MHz) δ: Rotamers 1.22 (t, 3H), 2.15, 2.47 (2xs, 3H), 2.97, 3.16 (2xs, 3H), 3.21 (s, 3H), 3.22 (s, 3H), 3.65 (q, 2H), 3.90 (m, 2H), 4.68 (m, 2H), 4.77, 4.84 (2xs, 2H), 8.37 (d, 1H), 8.56 (d, 1H), 8.78 (d, 1H).

MS APCI+ m/z 414 $[MH]^+$

Example 17

1-(2-ethoxyethyl)-N^5,N^5-dimethyl-3-(methylaminomethyl)-N^7-(pyrazin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine hydrochloride



A mixture of the chloride from preparation 33 (109mg, 0.3mmol), dimethylamine (33% in ethanol, 0.27ml, 1.5mmol) and N,N-diisopropylethylamine (0.26ml, 1.5mmol) in 1-methyl-2-pyrrolidinone (1mL) was heated at 120°C for 18 hours in a ReactiVial™. The cooled mixture was evaporated *in vacuo* and the residue purified by column chromatography on silica gel using

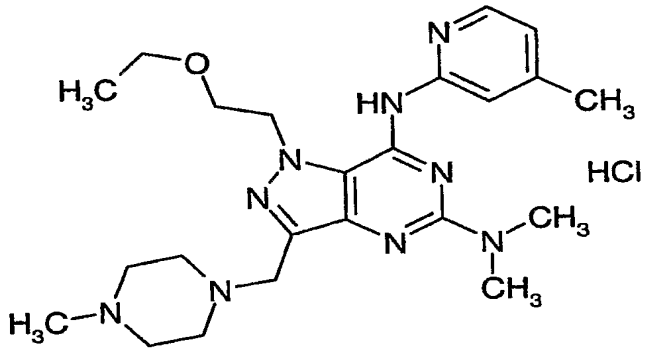
dichloromethane:methanol:ammonium hydroxide (98:2:0.2) as eluant. The product was dissolved in dichloromethane, 2M hydrogen chloride in ether (0.037mL, 0.074mmol) added and the solution evaporated *in vacuo* to afford the title compound, 23mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.20 (t, 3H), 2.62 (s, 3H), 3.23 (s, 6H), 3.66 (q, 2H), 3.92 (t, 2H), 4.19 (s, 2H), 4.73 (t, 2H), 7.04 (s, 1H), 8.24 (d, 1H), 8.38 (d, 1H)

MS APCI+ m/z 372 $[MH]^+$

Example 18

1-(2-Ethoxyethyl)-N^5,N^5-dimethyl-3-[(4-methylpiperazin-1-yl)methyl]-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine hydrochloride



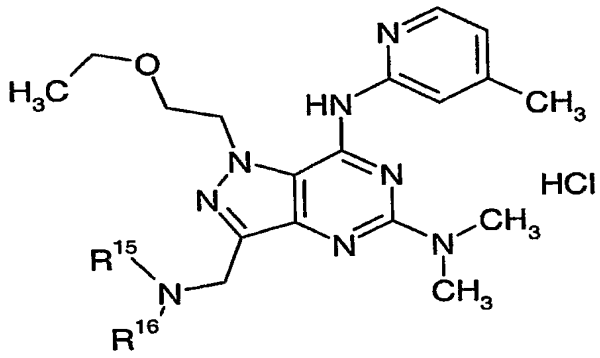
The aldehyde of preparation 39 (75mg, 0.2mmol), sodium triacetoxyborohydride (52mg, 0.24mmol) and 1-methylpiperazine (73mg, 0.73mmol) were dissolved in dichloromethane (15mL). The reaction mixture was stirred at room temperature for 2 hours and was then treated with sodium bicarbonate solution (8mL) and extracted with dichloromethane (3x15mL). The organics were combined, concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 90:10. The product was treated with 2M hydrogen chloride in ether (0.1mL), the mixture concentrated and the product dried *in vacuo*, to afford the title compound as a yellow crystalline solid, 29.6mg.

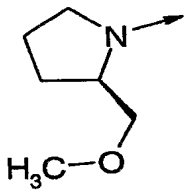
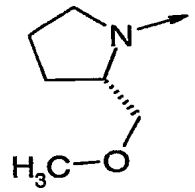
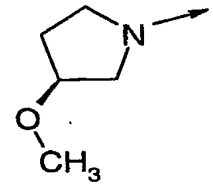
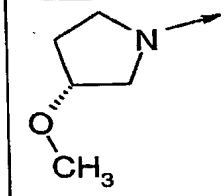
^{1}H NMR (D_2O, 400MHz) δ: 0.80 (t, 3H), 2.30 (s, 3H), 2.50 (br m, 2H), 2.72 (s, 3H), 3.00 (br m, 4H), 3.06 (s, 6H), 3.38 (m, 4H), 3.80 (m, 4H), 4.75 (t, 2H), 7.00 (d, 1H), 7.55 (s, 1H), 7.84 (d, 1H).

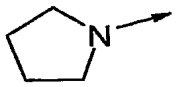
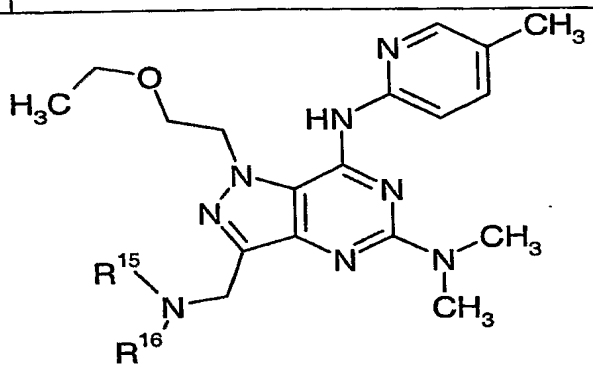
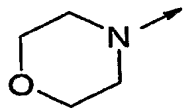
MS APCI+ m/z 454 $[MH]^+$

Examples 19 - 27

The following compounds, of the general formula shown below, were prepared by a method similar to that described for example 18 using the appropriate $HNR^{15}R^{16}$ amine and the appropriate aldehyde of preparations 39 and 40.

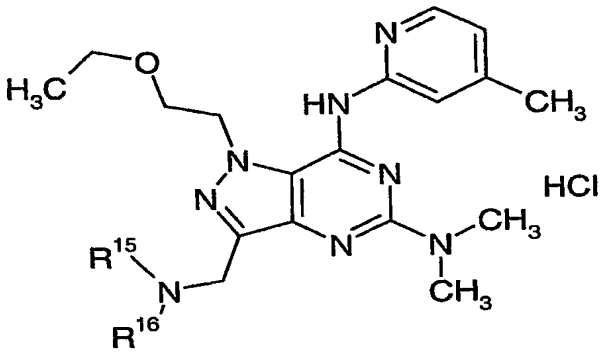


No.	$NR^{15}R^{16}$	Data
19		^{1}H NMR (D_2O, 400MHz) δ: 0.65 (t, 3H), 1.72 (m, 1H), 1.85 (m, 2H), 2.08 (m, 1H), 2.15 (s, 3H), 2.94 (s, 6H), 3.08 (s, 3H), 3.24 (m, 1H), 3.35 (m, 2H), 3.40 (m, 3H), 3.75 (m, 3H), 4.45 (m, 2H), 4.58 (m, 2H), 6.82 (d, 1H), 7.70 (m, 1H), 7.90 (d, 1H). MS APCI+ m/z 469 $[MH]^+$
20		^{1}H NMR (D_2O, 400MHz) δ: 0.75 (t, 3H), 1.70-2.08 (m, 3H), 2.18 (s, 3H), 2.59 (s, 6H), 3.10 (s, 3H), 3.20-3.47 (m, 6H), 3.77 (m, 3H), 4.40-4.70 (m, 5H), 6.62 (d, 1H), 7.70 (m, 1H), 7.90 (d, 1H). MS APCI+ m/z 469 $[MH]^+$
21		^{1}H NMR (D_2O, 400MHz) δ: 0.82 (t, 3H), 2.10 (m, 2H), 2.35 (s, 3H), 3.10 (s, 6H), 3.18 (s, 3H), 3.40-3.50 (m, 6H), 3.85 (t, 2H), 4.15 (m, 1H), 4.60 (m, 2H), 4.80 (m, 2H), 7.05 (d, 1H), 7.59 (s, 1H), 7.99 (d, 1H). MS APCI+ m/z 455 $[MH]^+$
22		^{1}H NMR (D_2O, 400MHz) δ: 0.82 (t, 3H), 2.35 (s, 3H), 3.10 (s, 6H), 3.18 (s, 3H), 3.40-3.50 (m, 6H), 3.80 (t, 2H), 4.15 (m, 1H), 4.61 (m, 2H), 4.82 (m, 2H), 7.10 (d, 1H), 7.59 (s, 1H), 7.99 (d, 1H). MS APCI+ m/z 455 $[MH]^+$

23	$(CH_3)_2CHNH$-	^{1}H NMR (D_2O, 400MHz) δ: 0.83 (t, 3H), 1.27 (d, 6H), 2.26 (s, 3H), 3.06 (s, 6H), 3.41 (m, 3H), 3.80 (t, 2H), 4.36 (s, 2H), 4.69 (m, 2H), 6.94 (d, 1H), 7.61 (m, 1H), 7.93 (d, 1H). MS APCI+ m/z 427 $[MH]^+$ ***CHECK THIS***
24	$CH_3(CH_2)_2NH$-	^{1}H NMR (D_2O, 400MHz) δ: 0.83 (m, 6H), 1.60 (m, 2H), 2.26 (s, 3H), 2.97 (t, 2H), 3.06 (s, 6H), 3.40 (q, 2H), 3.80 (t, 2H), 4.35 (s, 2H), 4.70 (m, 2H), 6.94 (d, 1H), 7.62 (m, 1H), 7.93 (d, 1H). MS APCI+ m/z 413 $[MH]^+$
25		^{1}H NMR (D_2O, 400MHz) δ: 0.86 (t, 3H), 2.02 (m, 4H), 2.35 (s, 3H), 3.15 (s, 6H), 3.18 (m, 2H), 3.40 (q, 2H), 3.45 (m, 2H), 3.84 (t, 2H), 4.55 (s, 2H), 4.81 (t, 2H), 7.03 (d, 1H), 7.57 (s, 1H), 7.96 (d, 1H). MS APCI+ m/z 425 $[MH]^+$
		
26	CH_3CH_2NH-	^{1}H NMR (CD_3OD, 400MHz) δ: 1.11 (t, 3H), 1.21 (t, 3H), 2.32 (s, 3H), 2.84 (q, 2H), 3.21 (s, 6H), 3.60 (q, 2H), 3.86 (m, 2H), 4.09 (s, 2H), 4.71 (m, 2H), 7.63 (d, 1H), 8.16 (m, 1H), 8.37 (m, 1H). MS APCI+ m/z 399 $[MH]^+$
27		^{1}H NMR (CD_3OD, 400MHz) δ: 1.08 (t, 3H), 2.28 (s, 3H), 2.64 (m, 4H), 3.21 (s, 6H), 3.59 (q, 2H), 3.68 (m, 4H), 3.86 (s, 2H), 3.89 (m, 2H), 4.69 (m, 2H), 7.63 (d, 1H), 8.16 (s, 1H), 8.37 (d, 1H). MS APCI+ m/z 441 $[MH]^+$

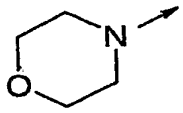
- Example 21 – The product of preparation 46 was used as the $HNR^{15}R^{16}$ amine
- Example 22 - The product of preparation 45 was used as the $HNR^{15}R^{16}$ amine

Examples 28 – 31



The bromo compound of preparation 19 (76mg, 0.18mmol) was dissolved in 1-methyl-2-pyrrolidinone (150μL) and the solution treated with the appropriate $HNR^{15}R^{16}$ amine (1.78mmol). The reaction mixture was stirred at 60°C for 2 hours and then concentrated to low volume *in vacuo*. A 33% solution of dimethylamine (0.18mmol) in ethanol was added and the reaction mixture sealed in a ReactiVial™ and heated to 120°C for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (1mL) and saturated sodium bicarbonate solution (1mL). The organic layer was separated and purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia 100:0:0 to 90:10:1. The residues were treated with 2M hydrogen chloride in ether (30μL), and the mixtures evaporated *in vacuo* to afford the title compounds.

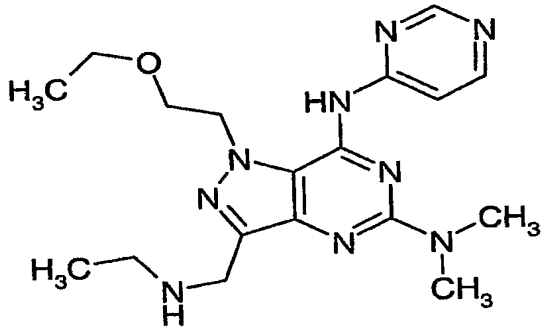
No	$NR^{15}R^{16}$	Data
28	$(CH_3)_2N$-	^{1}H NMR (D_2O, 400MHz) δ: 0.80 (t, 3H), 2.22 (s, 3H), 2.80 (s, 6H), 3.04 (s, 6H), 3.40 (q, 2H), 3.81 (t, 2H), 4.43 (s, 2H), 4.75 (m, 2H), 6.93 (d, 1H), 7.70 (m, 1H), 7.96 (d, 1H). MS APCI+ m/z 399 $[MH]^+$
29	$CH_3O(CH_2)_2NH$-	^{1}H NMR (D_2O, 400MHz) δ: 0.85 (t, 3H), 2.32 (s, 3H), 3.11 (m, 6H), 3.23 (t, 2H), 3.27 (s, 3H), 3.43 (q, 2H), 3.63 (t, 2H), 3.85 (t, 2H), 4.43 (s, 2H), 4.79 (m, 2H), 7.02 (d, 1H), 7.59 (s, 1H), 7.96 (d, 1H). MS APCI+ m/z 429 $[MH]^+$

30		^{1}H NMR (D_2O, 400MHz) δ: 0.82 (t, 3H), 2.31 (s, 3H), 3.08 (m, 6H), 3.14 (m, 4H), 3.41 (q, 2H), 3.80 (m, 6H), 4.37 (m, 2H), 4.75 (m, 2H), 6.98 (d, 1H), 7.65 (s, 1H), 7.96 (d, 1H). MS APCI+ m/z 441 $[MH]^+$
31	CH_3CH_2NH-	^{1}H NMR (CD_3OD, 400MHz) δ: 1.10 (t, 3H), 1.37 (t, 3H), 2.40 (s, 3H), 3.23 (q, 2H), 3.26 (s, 6H), 3.60 (q, 2H), 3.91 (t, 2H), 4.45 (s, 2H), 4.78 (m, 2H), 6.96 (d, 1H), 8.17 (d, 1H), 8.38 (s, 1H). MS APCI+ m/z 399 $[MH]^+$

- Example 28 – Used a 33% solution of dimethylamine in ethanol as the source of the $HNR^{15}R^{16}$amine
- Example 31 – Used a 2M solution of ethylamine in methanol as the source of the $HNR^{15}R^{16}$amine

Example 32

1-(2-ethoxyethyl)-3-(ethylaminomethyl)-*N*^{5},*N*^{5}-dimethyl-*N*^{7}-(pyrimidin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine



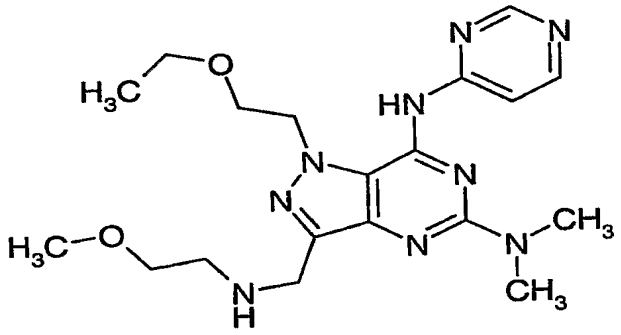
The aldehyde of preparation 41 (50mg, 0.14mmol) was dissolved in dichloromethane (2mL) and the solution treated with ethylamine hydrochloride (13mg, 0.15mmol), sodium triacetoxyborohydride (45mg, 0.21mmol) and triethylamine (20μL, 0.15mmol). The mixture was stirred at room temperature for 30 minutes and was then treated with additional ethylamine hydrochloride (13mg, 0.15mmol) and triethylamine (20μL, 0.15mmol) and stirred for a further 30 minutes. The mixture was then treated with a 2M solution of ethylamine in ethanol (160μL) and tetrahydrofuran (1mL) and stirred at room temperature for 1 hour. The reaction mixture was partitioned between saturated sodium hydrogencarbonate solution (20mL) and dichloromethane (20mL) and the

aqueous was extracted with dichloromethane (20mL). The organics were combined, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia 90:10:1 to yield the title product, 29mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.18 (m, 6H), 2.78 (q, 2H), 3.23 (s, 6H), 3.63 (q, 2H), 3.90 (m, 2H), 4.69 (m, 2H), 4.85 (s, 2H), 8.40 (m, 1H), 8.56 (d, 1H), 8.79 (s, 1H). MS APCI+ m/z 386 $[MH]^+$

Example 33

1-(2-ethoxyethyl)-3-[(2-methoxyethylamino)methyl]-*N*^{5},*N*^{5}-dimethyl-*N*^{7}-pyrimidin-4-yl-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine

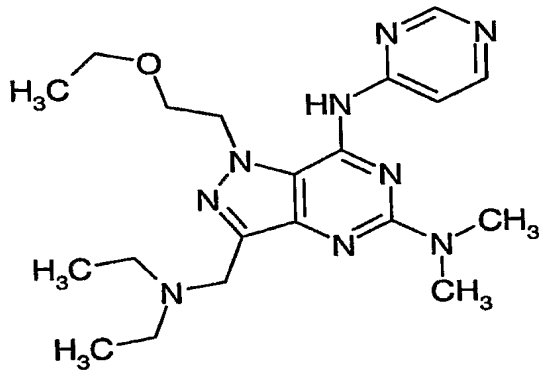


The title product was prepared by a method similar to that described in example 32 using 2-methoxyethylamine and the aldehyde of preparation 41.

^{1}H NMR (CD_3OD, 400MHz) δ:1.20 (t, 3H), 2.90 (t, 2H), 3.23 (s, 6H), 3.34 (s, 3H), 3.55 (m, 2H), 3.63 (q, 2H), 3.91 (m, 2H), 4.09 (s, 2H), 4.68 (m, 2H), 8.38 (m, 1H), 8.58 (d, 1H), 8.79 (s, 1H). MS APCI+ m/z 416 $[MH]^+$

Example 34

3-(Diethylaminomethyl)-1-(2-ethoxyethyl)-N^6,N^6-dimethyl-N^7-(pyrimidin-4-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine

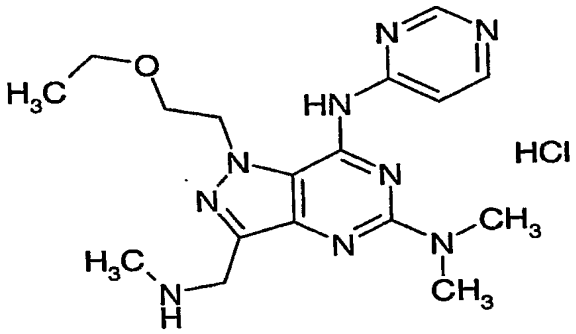


The chloro compound of preparation 21 (60mg, 0.15mmol) was dissolved in dimethyl sulphoxide (2mL) and the solution treated with N-ethyldiisopropylamine (129µL, 0.74mmol) and a 33% solution of dimethylamine in ethanol (133µL, 0.74mmol). The reaction mixture was sealed in a ReactiVial™ and heated to 120°C for 18 hours. The reaction mixture was partitioned between ethyl acetate and water and the aqueous extracted with ethyl acetate (x3). The organics were combined and washed with water and brine, dried over magnesium sulphate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol 95:5 to 90:10 to yield the title product, 29mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 1.24 (t, 6H), 1.42 (t, 3H), 2.86 (q, 2H), 3.22 (s, 6H), 3.65 (q, 2H), 3.92 (t, 2H), 4.25 (s, 4H), 4.68 (t, 2H), 8.32 (d, 1H), 8.58 (d, 1H), 8.86 (s, 1H). MS ES+ m/z 414 $[MH]^+$

Example 35

1-(2-ethoxyethyl)-N^6,N^6-dimethyl-3-(methylaminomethyl)-N^7-pyrimidin-4-yl-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine hydrochloride



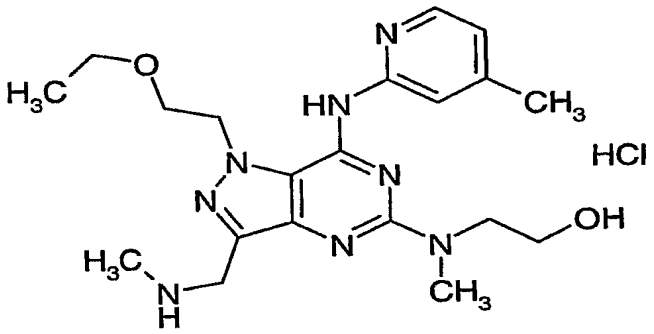
The chloro compound of preparation 32 (32mg, 0.09mmol) was added to a mixture of a 33% solution of dimethylamine in ethanol (60µL, 0.45mmol) and N-ethyldiisopropylamine (80µL, 0.45mmol) in 1-methyl-2-pyrrolidinone (1mL). The reaction mixture was heated to 120°C for 18 hours in a ReactiVial™ and was then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with dichloromethane:methanol:0.88 ammonia 90:10:1. The crude product was dissolved in dichloromethane and treated with ethereal 2M hydrogen chloride and then concentrated *in vacuo* to yield the title product, 9mg.

^{1}H NMR (CD_3OD, 400MHz) δ: 1.21 (t, 3H), 2.63 (s, 3H), 3.24 (s, 6H), 3.64 (q, 2H), 3.92 (m, 2H), 4.21 (s, 2H), 4.73 (m, 2H), 8.36 (s, 1H), 8.58 (d, 1H), 8.81 (s, 1H)

MS APCI+ m/z 372 $[MH]^+$

Example 36

2-{[1-(2-ethoxyethyl)-3-(methylaminomethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl]methylamino}ethanol hydrochloride

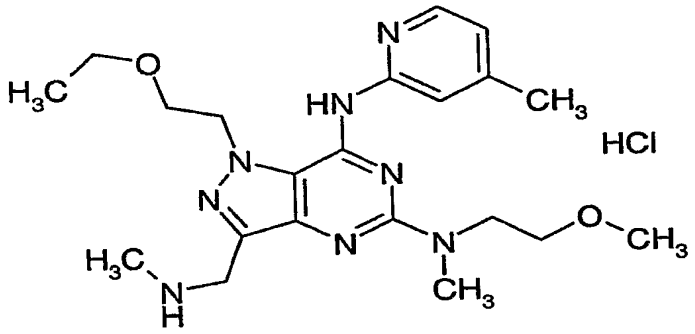


The BOC protected amine of preparation 35 (66.5mg, 0.14mmol) was dissolved in dimethyl sulphoxide (1.5mL) and the solution treated with 2-(methylamino)ethanol (56µL, 0.70mmol) and N-ethyldiisopropylamine (120µL, 0.70mmol). The reaction mixture was sealed in a ReactiVial™ and heated to 120°C for 18 hours and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (5mL) and the solution treated with trifluoroacetic acid (1mL) and stirred for 1 hour at room temperature. The mixture was concentrated *in vacuo* and the residue partitioned between dichloromethane (10mL) and saturated sodium bicarbonate solution (10mL). The organic layer was separated and purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 97:3. The crude product was dissolved in dichloromethane, treated with 2M ethereal hydrogen chloride (100µL) and concentrated *in vacuo* to yield the title product, 30mg.

^{1}H NMR (D_2O, 400MHz) δ: 0.85 (t, 3H), 2.37 (s, 3H), 2.65 (s, 3H), 3.14 (s, 3H), 3.42 (q, 2H), 3.72 (m, 2H), 3.78 (m, 2H), 3.85 (t, 2H), 4.40 (s, 2H), 4.80 (t, 2H), 7.08 (d, 1H), 7.48 (s, 1H), 7.95 (d, 1H). MS APCI+ m/z 415 $[MH]^+$

Example 37

1-(2-ethoxyethyl)-N^5-(2-methoxyethyl)-N^5-methyl-3-(methylaminomethyl)-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine hydrochloride

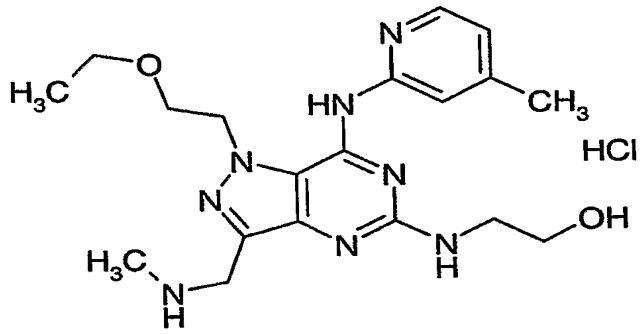


The title product was prepared by a method similar to that described for example 36 using N-(2-methoxyethyl)methylamine and the BOC protected amine of preparation 35.

^{1}H NMR (D_2O, 400MHz) δ: 0.85 (t, 3H), 2.37 (s, 3H), 2.65 (s, 3H), 3.14 (s, 3H), 3.22 (s, 3H), 3.44 (q, 2H), 3.65 (t, 2H), 3.78 (t, 2H), 3.87 (t, 2H), 4.40 (s, 2H), 4.82 (t, 2H), 7.10 (d, 1H), 7.49 (s, 1H), 7.95 (d, 1H). MS APCI+ m/z 429 $[MH]^+$

Example 38

2-[1-(2-ethoxyethyl)-3-(methylaminomethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-ylamino]ethanol

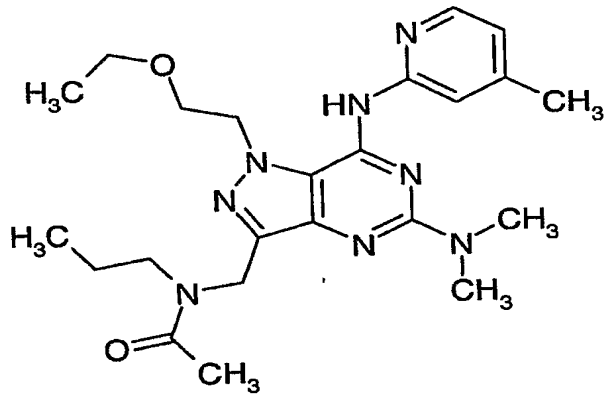


The title product was prepared by a method similar to that described for example 36 using ethanolamine and the protected amine of preparation 35.

^{1}H NMR (D_2O, 400MHz) δ: 0.80 (t, 3H), 2.35 (s, 3H), 2.62 (s, 3H), 3.40 (m, 4H), 3.65 (m, 2H), 3.82 (t, 2H), 4.33 (s, 2H), 4.78 (t, 2H), 7.05 (d, 1H), 7.42 (s, 1H), 7.95 (d, 1H). MS APCI+ m/z 402 $[MH]^+$

Example 39

N-[5-Dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-propylacetamide

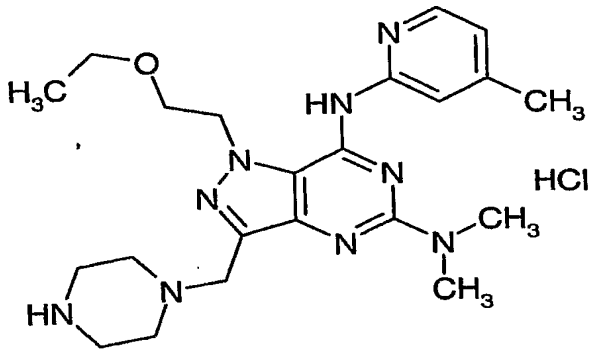


The product of example 24 (30mg, 0.07mmol) was added to a solution of triethylamine (10µL, 0.09mmol) in dichloromethane (1mL) and the mixture treated with acetyl chloride (8µL, 0.09mmol). The reaction mixture was stirred at room temperature for 18 hours and then concentrated *in vacuo*. The residue was dissolved in methanol (2mL) and washed with 2M sodium hydroxide solution (10mL) and water (10mL). The solution was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water, the organic phase was dried over magnesium sulphate and purified by column chromatography on silica gel eluting with dichloromethane:methanol:ammonium hydroxide 98:2:0.2 to yield the title product, 10mg.

^{1}H NMR ($CDCl_3$, 400MHz) δ: 0.90 (t, 3H), 1.15 (t, 3H), 1.65 (m, 2H), 2.19 (s, 3H), 2.42 (s, 3H), 3.32 (s, 6H), 3.59 (q, 2H), 3.85 (t, 2H), 4.59 (s, 2H), 4.79 (s, 2H), 4.82 (t, 2H), 6.95 (d, 1H), 7.75 (s, 1H), 8.27 (d, 1H), 10.60 (s, 1H). MS APCI+ m/z 455 $[MH]^+$

Example 40

1-(2-ethoxyethyl)-N^5,N^5-dimethyl-N^7-(4-methylpyridin-2-yl)-3-(piperazin-1-ylmethyl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine hydrochloride



The protected amine of preparation 42 (80mg, 0.15mmol) was dissolved in 10% solution of trifluoroacetic acid in dichloromethane (5mL) and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue purified by column chromatography on silica gel eluting with dichloromethane:methanol 100:0 to 90:10. The crude product was treated with 2M hydrogen chloride in ether (100μL) and concentrated *in vacuo* to yield the title product, 33mg.

^{1}H NMR (D_2O, 400MHz) δ: 0.70 (t, 3H), 1.80 (s, 3H), 2.50 (m, 4H), 2.70 (m, 6H), 2.80 (m, 4H), 3.30 (q, 2H), 3.55 (s, 2H), 3.65 (m, 2H), 4.30 (m, 2H), 6.65 (m, 1H), 7.80 (m, 2H). MS APCI+ m/z 440 $[MH]^+$

Assay

The compounds of the invention are inhibitors of cyclic guanylate monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5 inhibitors). Preferred compounds suitable for use in accordance with the present invention are potent and selective PDE5 inhibitors. *In vitro* PDE inhibitory activities against cyclic guanosine 3',5'-monophosphate (cGMP) and cyclic adenosine 3',5'-monophosphate (cAMP) phosphodiesterases can be determined by measurement of their IC_{50} values (the concentration of compound required for 50% inhibition of enzyme activity).

The required PDE enzymes can be isolated from a variety of sources, including human corpus cavernosum, human and rabbit platelets, human cardiac ventricle, human skeletal muscle and bovine retina, essentially by a modification of the method of Thompson, WJ *et al.*; Biochemistry 18(23), 5228-5237, 1979, as described by Ballard SA et al.; J. Urology 159(6), 2164-2171, 1998. In particular, cGMP-specific PDE5 and cGMP-inhibited cAMP PDE3 can be obtained from human corpus cavernosum tissue, human platelets or rabbit platelets; cGMP-stimulated PDE2 was obtained from human corpus cavernosum; calcium/calmodulin (Ca/CAM)-dependent PDE1 from human cardiac ventricle; cAMP-specific PDE4 from human skeletal muscle; and photoreceptor PDE6 from bovine retina. Phosphodiesterases 7-11 can be generated from full length human recombinant clones transfected into SF9 cells.

Assays can be performed either using a modification of the "batch" method of Thompson WJ and Appleman MM; Biochemistry 10(2),311-316, 1971, essentially as described by Ballard SA et al.; J. Urology 159(6), 2164-2171, 1998, or using a scintillation proximity assay for the direct detection of [^{3}H]-labelled AMP/GMP using a modification of the protocol described by Amersham plc under product code TRKQ7090/7100. In summary, for the scintillation proximity assay the effect of PDE inhibitors was investigated by assaying a fixed amount of enzyme in the presence of varying inhibitor concentrations and low substrate, (cGMP or cAMP in a 3:1 ratio unlabelled to [^{3}H]-labeled at a concentration of ~1/3 K_m or less) such that $IC_{50} \cong K_i$. The final assay volume was made up to 100µl with assay buffer [20mM Tris-HCl pH 7.4, 5mM $MgCl_2$, 1mg/ml bovine serum albumin]. Reactions were initiated with enzyme, incubated for 30-60min at 30°C to give <30% substrate turnover and terminated with 50µl yttrium silicate SPA beads (containing 3mM of the respective unlabelled cyclic nucleotide for PDEs 9 and 11). Plates were re-sealed and shaken for 20min, after which the beads were allowed to settle for 30min in the dark and then counted on a TopCount plate reader (Packard, Meriden, CT) Radioactivity units were converted to % activity of an uninhibited control (100%), plotted against inhibitor concentration and inhibitor IC_{50} values obtained using the 'Fit Curve' Microsoft Excel extension.

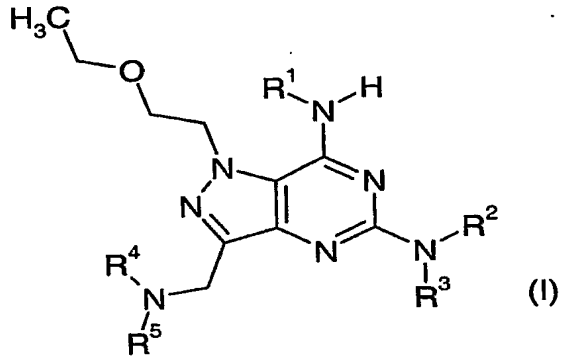
All compounds of the invention have an activity against PDE-5 of less than 10,000nM. IC_{50} values for representative preferred compounds are listed in the table below.

Example	IC_{50} (nM)	Example	IC_{50} (nM)
1	1.12	11	0.53
2	1.25	15	0.48
4	0.77	18	2.30
6	0.39	30	1.06
8	0.59	31	3.40
9	0.33		

5

Claims

1. A compound of formula (I)



(I)

wherein

R^1 is a cyclic group R^A which is optionally substituted with one or more C_1-C_3 alkyl groups;

R^2 and R^3 are each independently hydrogen or C_1-C_3 alkyl optionally substituted with a group selected from OH and OCH_3;

R^4 is selected from R^6, $R^6C(O)$ and R^6SO_2, and

R^5 is selected from hydrogen and C_1-C_3 alkyl,

or $-NR^4R^5$ constitutes a 5- or 6-membered saturated ring which may optionally include one further heteroatom selected from nitrogen and oxygen, and which may optionally be substituted with a group selected from methyl, methoxy and methoxymethyl;

R^6 is selected from C_1-C_3 alkyl optionally substituted a group selected from hydroxy, methoxy and dimethylamino; and

R^A is a 6-membered heteroaromatic ring containing one or two nitrogen atoms;

a tautomer thereof or a pharmaceutically acceptable salt, solvate or polymorph of said compound or tautomer.

2. A compound according to claim 1 wherein R^1 is a cyclic group R^A which is optionally substituted with a methyl group.

3. A compound according to claim 1 or 2 wherein R^A is pyridyl, pyrimidyl or pyrazinyl.

4. A compound according to any one of claims 1 to 3 wherein R^2 is C_1-C_3 alkyl optionally substituted with a group selected from OH and OCH_3 and R^3 hydrogen or C_1-C_3 alkyl.

5. A compound according to claim 4 wherein R^2 is methyl or ethyl optionally substituted at the 2-position with a group selected from OH and OCH_3.

6. A compound according to claim 4 or 5 wherein R^3 is hydrogen or methyl.

7. A compound according to any one of claims 1 to 6 wherein R^4 is selected from R^6, $R^6C(O)$ and R^6SO_2 and R^5 is selected from hydrogen and C_1-C_3 alkyl.

8. A compound according to claim 7 wherein R^4 is R^6 and R^6 is C_1-C_3 alkyl or 2-methoxyethyl.

9. A compound according to claim 7 wherein R^4 is $R^6C(O)$ and R^6 is selected from methyl, ethyl, hydroxymethyl and dimethylaminomethyl.

10. A compound according to claim 7 wherein R^4 is R^6SO_2 and R^6 is methyl.

11. A compound according to any one of claims 1 to 6 wherein $-NR^4R^5$ constitutes a 5- or 6-membered saturated ring which may optionally include one further heteroatom selected from nitrogen and oxygen, and which may optionally be substituted with a group selected from methyl, methoxy and methoxymethyl.

12. A compound according to claim 11 wherein -NR^4R^5 constitutes a pyrrolidine, morpholine or piperazine ring optionally be substituted with a group selected from methyl, methoxy and methoxymethyl.

13. A compound according to claim 1 selected from:

2-dimethylamino-*N*-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]methanesulfonamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-2-hydroxyacetamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide,

N-[1-(2-ethoxyethyl)-5-ethylamino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]acetamide,

N-[5-dimethylamino-1-(2-ethoxyethyl)-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]propionamide,

N-[1-(2-ethoxyethyl)-5-ethylamino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]propionamide,

N-[1-(2-ethoxyethyl)-5-ethylamino-7-(4-methylpyridin-2-ylamino)-1*H*-pyrazolo[4,3-*d*]pyrimidin-3-ylmethyl]-*N*-methylacetamide,

1-(2-ethoxyethyl)-N^5,N^5-dimethyl-3-[(4-methylpiperazin-1-yl)methyl]-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine,

1-(2-ethoxyethyl)-N^5,N^5-dimethyl-3-[(4-morpholino)methyl]-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine, and

1-(2-ethoxyethyl)-3-(ethylaminomethyl)-N^5,N^5-dimethyl-N^7-(4-methylpyridin-2-yl)-1*H*-pyrazolo[4,3-*d*]pyrimidine-5,7-diamine

and tautomers thereof and pharmaceutically acceptable salts, solvates and polymorphs of said compounds or tautomers.

14. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 13, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a pharmaceutically acceptable diluent or carrier.

15. A compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use as a medicament.

16. A compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in accordance with claim 15 as a medicament for the treatment of a disease or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

17. A compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof, for use in accordance with claim 15 or 16 as a medicament for the treatment of a disease or condition selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal

disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

18. A method of treatment of a disorder or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect, in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof.

19. A method according to claim 18, wherein the disorder or condition is selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis,

skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

20. Use of a compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament for the treatment of a disorder or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

21. Use according to claim 20, wherein the disorder or condition is selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

22. Use according to claim 21 wherein the disorder or condition is hypertension.

23. Use according to claim 22 wherein the disorder or condition is selected from essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension.

24. Use according to claim 21 wherein the disorder or condition is diabetes.

25. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 13, or pharmaceutically acceptable salts, solvates or polymorphs thereof, and a second pharmaceutically active agent selected from aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), CI1027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid).

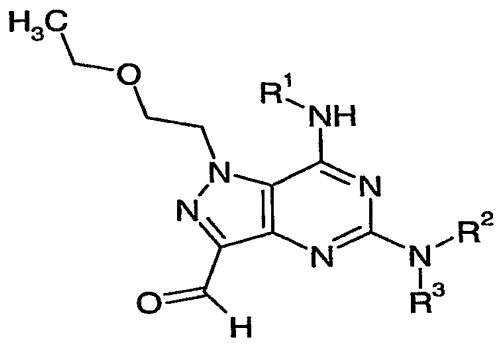
26. Use of a compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament combined with a second pharmaceutically active agent selected from aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), CI1027, CCR5 receptor antagonists,

imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid), for the treatment of a disease or condition where inhibition of PDE5 is known, or can be shown, to produce a beneficial effect.

27. Use according to claim 26 of a compound of formula (I) as claimed in any one of claims 1 to 13, or a pharmaceutically acceptable salt, solvate or polymorph thereof, in the preparation of a medicament combined with a second pharmaceutically active agent selected from aspirin, angiotensin II receptor antagonists (such as losartan, candesartan, telmisartan, valsartan, irbesartan and eprosartan), calcium channel blockers (such as amlodipine), beta-blockers (i.e. beta-adrenergic receptor antagonists such as sotalol, propranolol, timolol, atenolol, carvedilol and metoprolol), CI1027, CCR5 receptor antagonists, imidazolines, sGCa's (soluble guanylate cyclase activators) antihypertensive agents, diuretics (such as hydrochlorothiazide, torsemide, chlorothiazide, chlorthalidone and amiloride), alpha adrenergic antagonists (such as doxazosin), ACE (angiotensin converting enzyme) inhibitors (such as quinapril, enalapril, ramipril and lisinopril), aldosterone receptor antagonists (such as eplerenone and spironolactone), neutral endopeptidase inhibitors, antidiabetic agents (such as insulin, sulfonylureas (such as glyburide, glipizide and glimepiride), glitazones (such as rosiglitazone and pioglitazone) and metformin), cholesterol lowering agents (such as atorvastatin, pravastatin, lovastatin, simvastatin, clofibrate and rosuvastatin), and

alpha-2-delta ligands (such as gabapentin, pregabalin, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (1α,3α,5α)-(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid and (3S,5R)-3-amino-5-methyl-octanoic acid), for the treatment of a disease or condition is selected from hypertension (including essential hypertension, pulmonary hypertension, secondary hypertension, isolated systolic hypertension, hypertension associated with diabetes, hypertension associated with atherosclerosis, and renovascular hypertension), congestive heart failure, angina (including stable, unstable and variant (Prinzmetal) angina), stroke, coronary artery disease, congestive heart failure, conditions of reduced blood vessel patency (such as post-percutaneous coronary angioplasty), peripheral vascular disease, atherosclerosis, nitrate-induced tolerance, nitrate tolerance, diabetes, impaired glucose tolerance, metabolic syndrome, obesity, sexual dysfunction (including male erectile disorder, impotence, female sexual arousal disorder, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual pain disorder, female sexual orgasmic dysfunction and sexual dysfunction due to spinal cord injury), premature labour, pre-eclampsia, dysmenorrhea, polycystic ovary syndrome, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, chronic obstructive pulmonary disease, acute respiratory failure, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, gut motility disorders (including irritable bowel syndrome), Kawasaki's syndrome, multiple sclerosis, Alzheimer's disease, psoriasis, skin necrosis, scarring, fibrosis, pain (particularly neuropathic pain), cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and haemorrhoids.

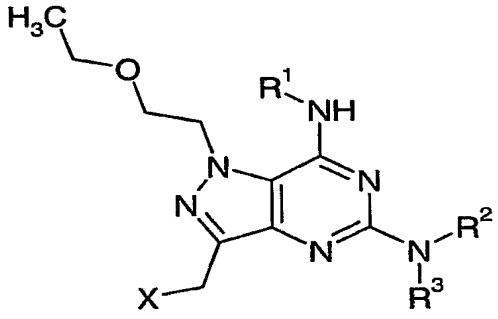
28. A compound of formula (III)



(III)

wherein R^1, R^2 and R^3 are as defined in claim 1.

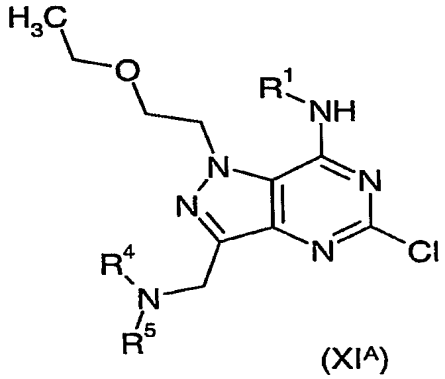
29. A compound of formula (IV)



(IV)

wherein R^1, R^2 and R^3 are as defined in claim 1 and X is Cl, Br or CH_3SO_2O-.

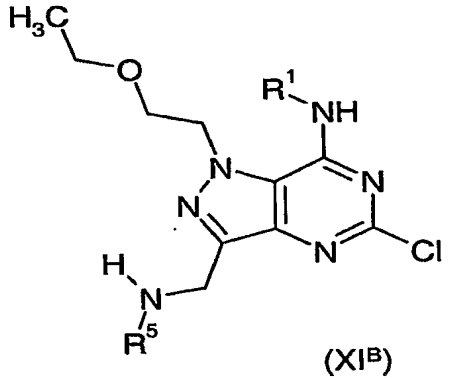
30. A compound of formula (XI^A)



(XI^A)

wherein R^1, R^4 and R^5 are as defined in claim 1.

31. A compound of formula (XI^B)



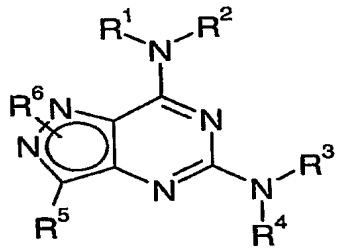
(XI^B)

wherein R^1 and R^5 are as defined in claim 1.

Abstract

Novel Pharmaceuticals

This invention relates to compounds of formula (I)



(I)